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PULMONARY HYPERTROPHIC OSTEOARTHROPATHY

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HYPERTROPHIC osteoarthropathy associated with intrathoracic disease is a syndrome consisting of: (*a*) nonpitting swelling of the tissues over the ends of the long bones (this swelling is usually warm and tender to the touch); (*b*) clubbing of the digits; and (*c*) the radiographic appearance of periosteal new-bone formation beginning at the distal ends of the long bones. Nowadays the thoracic lesion is usually primary carcinoma of the bronchus.

Some writers loosely identify clubbing of the digits with osteoarthropathy; but our investigation is limited to the pathogenesis of hypertrophic osteoarthropathy associated with intrathoracic disease. Clubbing of the digits is not an *essential* feature of this condition; and because clubbing may be associated with many other conditions, it is improbable that a hypothesis explaining the pathogenesis of pulmonary osteoarthropathy would adequately explain the causes of clubbing.

Various theories have been put forward to account for the association of a lesion in the thorax with a disorder of the limbs. These fall into two broad categories, humoral and neurogenic. Marie (1890) first suggested that a toxin from the diseased lung affects the peripheral tissues. Neurogenic theories have been supported by the observation that vagotomy may lead to prompt regression of the limb swelling and the pain (Flavell 1956). Various pulmonary vascular shunts—arteriovenous (Hall 1959), venoarterial (Cudkowicz and Armstrong 1953, Doyle 1959), and bronchopulmonary anastomoses (Cudkowicz et al. 1960)—have been described in cases with clubbed fingers, and sometimes with osteoarthropathy, but their significance is not known.

Osteoarthropathy in dogs has provided us with an opportunity to extend our knowledge of the pathogenesis of this disorder. The dog appears to be more susceptible to osteoarthropathy than man. Between 1951 and 1960 the records show that, whereas the diagnosis was confirmed by radiography in only eight of 169,891 patients seen at the University of Pennsylvania Hospital it was confirmed in twenty-four of 41,675 dogs seen at the University Veterinary Hospital. In the dog, osteoarthropathy usually first manifests itself by a painful swelling of the limbs (fig. 1), and the diagnosis is confirmed by the radiographic appearance of the bone (fig. 2). The associated intrathoracic condition is usually neoplastic metastases. Dogs show no change comparable with digital clubbing, and the periosteal reaction is more exuberant: otherwise the manifestations in the two species are similar.

Fig. 1—Swollen limbs of dog 1.

Ginsburg (1958) showed that in man osteoarthropathy may be associated with an increased blood-flow in the limbs. We have found this also true in dogs, and we shall show that this hyperæmia is promptly reduced by procedures which are followed by regression of the signs and symptoms of osteoarthropathy. In this account we have assumed that observations made on dogs with osteoarthropathy apply equally to the condition in man.

Materials and Methods

Table I gives a brief account of the five patients and seven dogs studied during the last 18 months.

Blood-flow to the limbs was measured by a mercury-in-rubber strain-gauge plethysmograph (Whitney 1953, Holling et al. 1961). In patient 5 we attempted to distinguish to which tissues in the limb the increased blood-flow was directed. The

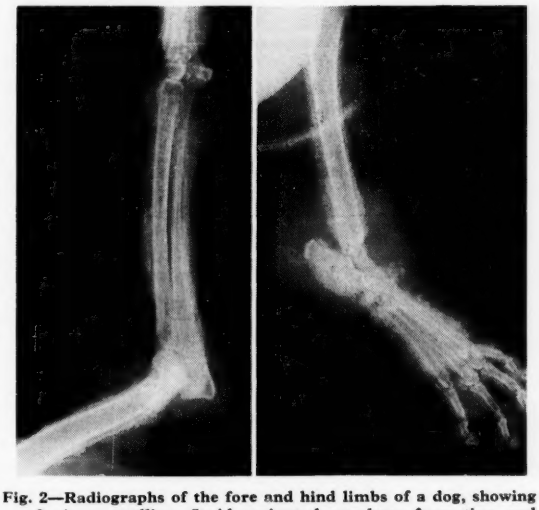

Fig. 2—Radiographs of the fore and hind limbs of a dog, showing soft tissue swelling, florid periosteal new-bone formation, and isolated foci of calcification in the soft tissues.

blood-flow to the calf was measured, and then the circulation to the skin and subcutaneous tissues was suppressed by iontophoresis of adrenaline (Cooper et al. 1955) and the blood-flow was remeasured; the difference between the two measurements indicates the proportion of the total blood-flow directed to the skin and subcutaneous tissues. The blood-flow to the iontophoresed calf was then measured simultaneously at two levels—one just below the knees, consisting mostly of bone and connective tissue, and the other in the mid calf, consisting mostly of muscular tissue—and the relative proportions of the constituent tissues at each level were estimated from a manual of cross-sectional anatomy (Eycleshymer and Schoemaker 1938). From the simultaneous blood-flow measurements and the assumed proportions of muscle and of bone and connective tissue at the two levels can be derived a pair of simultaneous equations, which, when solved, give an estimate of the blood-flow to these tissues. This procedure has given seemingly reasonable estimations of blood-flow to the different tissues, but further experience with it in normal and diseased states is desirable.

Blood-gas contents were measured by the Van Slyke manometric technique, and oxygen tension in arterial blood was measured with a modification of the Clark covered electrode (Polgar and Forster 1960). From analyses of arterial blood samples taken before and after breathing 100% oxygen for 12–20 minutes, the volume of pulmonary arteriovenous shunts was calculated by the method of Berggren (1942).

In the *cross-circulation* study the femoral artery and vein of a normal dog were connected by polyethylene tubing (I.D. 5·5 mm.) to those of a dog with osteoarthropathy, and vice versa.

Cardiac output was measured by a dye-dilution technique with cardiogreen.

Blood-pressure was recorded via a catheter inserted into the femoral artery by a ' Sanborn ' manometer (267B).

Results

Tissue Changes in Osteoarthropathy

Histological examination of the affected tissues was possible only in the dogs. An overgrowth of highly vascular connective tissue invested the tendons and bones in the distal parts of the limb (fig. 3). The tissue was composed of dense collagenous bundles supplied with many thick-walled blood-vessels (fig. 4). The tense swelling of the patients' limbs indicates a similar overgrowth of vascular connective tissue. Most of the new-bone formation was subperiosteal, but in areas of fibrochondroid metaplasia osteophytes sometimes formed without apparent contact with the underlying bone (fig. 2). No evidence of increased bone vascularity was noted. The synovial membranes of the adjacent joints showed only very slight changes.

Fig. 3—Flayed limbs of a normal dog (right), and one with osteoarthropathy (left), showing the overgrowth of highly vascular connective tissue in osteoarthropathy.

TABLE I—CLINICAL NOTES ON THE PATIENTS AND DOGS

Case	Age (yr.) and sex	Pulmonary condition	Presenting symptoms before diagnosis	Notes
Patient 1	63 M	Pleural mesothelioma	Pain and tenderness of ankles for 3 mos.	Finger-clubbing + + + Blood-flow in legs much increased Refused treatment
Patient 2	66 M	Inoperable bronchial carcinoma	Productive cough and dyspnœa for 2 yrs.	Finger-clubbing + + + Leg blood-flow fell from 7·1 to 1·7 ml. after chest exploration, with relief of ankle swelling and tenderness
Patient 3	56 M	Bronchial carcinoma	" Arthritis " of left ankle, hip, and thigh for 2 mos.	No finger-clubbing Osteoarthropathy diagnosed from X-rays No relief of lung tumour from irradiation or nitrogen mustard
Patient 4	58 M	Recurrence of bronchial carcinoma	Swelling and tenderness of ankles for 1 mo.	No finger-clubbing Prednisone relieved pain without reduction in hyperæmia
Patient 5	42 F	Adenosquamous carcinoma of rt. upper lobe	Swelling of shins and stiffness of knees for 1 yr.	Finger-clubbing + + + Intra-articular cortisone relieved pain and diminished blood-flow Osteoarthropathy relieved by pneumonectomy
Dog 1 (Boxer)	7 M	Lung metastases 7 mos. after hind-limb amputation for tibial osteosarcoma	Acute onset of osteoarthropathy; no respiratory signs	Unilateral vagotomy did not noticeably affect increased blood-flow during 12 days after operation
Dog 2 (Cocker spaniel)	12 F	Lung metastases from mammary carcinosarcoma	Osteoarthropathy and slight cough for 3 wks.	Blood-flow not measured Unilateral vagotomy relieved osteoarthropathy until death 5 days later
Dog 3 (Mongrel)	13 F	Lung metastases from mammary osteosarcoma	Osteoarthropathy for 1 wk.; no respiratory signs	Blood-flow in legs increased Died during operation just before vagotomy
Dog 4 (Mongrel)	8 F	Lung metastases from mammary adenocarcinoma	Osteoarthropathy for 1 mo.; no respiratory signs	Blood-flow was reduced after incision of parietal pleura and remained low during subsequent vagotomy
Dog 5 (Cocker spaniel)	13 F	Lung metastases from mammary osteosarcoma	Osteoarthropathy for 3 wks.; severe dyspnœa and cyanosis due to massive pleural effusion for 2 days	Blood-flow fell during periosteal rib-resection before unilateral vagotomy Blood-flow normal until death next day
Dog 6 (Boxer)	7 F (spayed)	Lung metastases from osteosarcoma of occipital bone	Cough for 1 mo., hæmoptysis for 2 wks.; osteoarthropathy found on clinical examination	Lumbar sympathectomy, cross-circulation study and atropinisation were each without effect on increased blood-flow Bilateral cervical vagotomy caused immediate reduction in blood-flow
Dog 7 (Boxer)	12 F	Bronchogenic adenocarcinoma of rt. diaphragmatic lobe with lung metastases	Cough for 6 mos.; osteoarthropathy for 6 wks.	Bretylium tosylate did not reduce blood-flow, which later fell when pedicle of affected lung was severed Blood-flow reached normal in 2 days, and remained so until death 6 wks. later

Sectional blood-flow to the affected parts of the limbs was increased in the three patients and six dogs in which it was measured (table II), and differential blood-flows were also estimated in one patient (table III).

All the patients, and all but one of the dogs, had some bone changes when the clinical diagnosis of osteoarthropathy was made. When first seen dog 1 showed the soft-tissue changes and greatly increased blood-flow typical of osteoarthropathy, but no radiographic evidence of periosteal proliferation. New-bone formation could be seen after 5 days, and it increased rapidly thereafter. The same sequence was seen in one other dog not included in this report. In patients 2, 4, and 5 swelling of the limb preceded the radiographic evidence of periosteal new-bone formation as the disorder extended into new areas.

Fig. 4—Histological section through a distal part of the leg of dog 1, showing numerous thick-walled blood-vessels in the connective tissue outside the periosteum (×40).

Procedures affecting Tissue Changes and Blood-flow

In patient 2 exploratory thoracotomy and hilar dissection was followed by diminution of the peripheral blood-flow (table I) and decrease in the limb swelling and digital clubbing. Radiological examination of the bones showed no definite change during the 6 weeks that this patient survived.

The bounding pulse of the clubbed fingers of patient 5 was not altered by ligation of the pulmonary artery to the affected lobe, but it disappeared as soon as the lung pedicle was severed.

TABLE III—EFFECT OF ADRENALINE IONTOPHORESIS ON CALF BLOOD-FLOW, DIFFERENTIAL BLOOD-FLOW TO CALF TISSUES, AND MEASUREMENT OF FINGER-CLUBBING IN A TREATED CASE (PATIENT 5) OF OSTEOARTHROPATHY)

—	Before operation	After operation		
		3 hours	5 days	7 weeks
Blood-flow (ml. blood per 100 ml. calf per min.):				
Before adrenaline iontophoresis	16·0	8·8	5·3	2·0
After „ „	8·2	4·7	3·7	1·0
Flow to skin and subcutaneous tissue	7·8	4·1	1·6	1·0
Estimated tissue flow (ml. blood per 100 ml. tissue per min.):				
Connective tissue and bone	10·6	6·8	1·4	0·8
Muscles	4·5	3·3	4·0	2·5
Circumference of terminal phalanx of left middle finger (cm.)	5·7	5·6	5·3	5·0

Immediately after operation the blood-flow to her limbs was greatly reduced (table III). During the next 5 days the limb blood-flows returned to normal, with diminution of the swelling of the limb and the finger-clubbing. 7 weeks after operation the swelling of the limbs had disappeared (fig. 5). The reduction in size of the limbs contrasted with the improvement in general nutrition which increased her body-weight by 10 lb. over this period; at this time resolution of the new-bone formation became apparent radiographically. After the operation adrenaline iontophoresis had a progressively smaller effect in reducing calf blood-flow. The estimation of blood-flows to the different tissues suggested that, in this patient, the increased blood-flow had been directed to skin and subcutaneous tissues, and to connective tissues and bone, rather than to the muscles (table III).

In the various dogs the increased blood-flow of the limbs fell at different stages of the surgical treatment of the pulmonary condition:

In dog 4 the increased blood-flow had fallen abruptly after the parietal pleura had been incised. Dog 5's blood-flow was reduced during the periosteal rib-resection, before the chest wall was opened (fig. 6); vagotomy was subsequently performed. The reduction in blood-flow persisted until the dog died next day.

In dog 7 (fig. 7) the blood-flow did not change until the pedicle of the affected lobe of the lung was severed; the blood-flow then sharply decreased, but it did not fall to normal levels until two days later. At this time the circumference of the carpal region was 2 cm. smaller. A week after operation the swelling of the limbs had disappeared. The periosteal changes were unaltered when the dog died from widespread lung metastases 6 weeks after lobectomy.

Thoracotomy in six normal dogs did not alter the peripheral blood-flow significantly unless it was accompanied by severe dislocation of the thoracic viscera and/or much blood-loss. The limb blood-flow was not reduced when a lung cancer was

TABLE II—SECTIONAL BLOOD-FLOW MEASUREMENTS IN HUMAN AND CANINE LIMBS

—	Ankle	Mid-calf	Upper calf	Thigh
Human studies:				
25 normal subjects (mean flow and S.D.)	4·06 (±3·0)	2·57 (±1·7)	2·32 (±1·2)	2·38 (±1·3)
Patient 3—right leg	6·2	3·3	4·2	..
—left leg	13·2	6·9	6·7	..
Patient 4—right leg	16·9	6·8	12·5	14·2
—left leg	19·5	7·3	8·4	8·7
Patient 5—right leg	17·0	10·0	11·0	8·0
—left leg	24·0	16·0	14·0	20·0
—	Metacarpal	Distal radius	Metatarsal	Distal tibia
Canine studies:				
15 normal dogs (mean flow and S.D.)	5·8 (±3·3)	7·7 (±4·7)	7·2 (±4·6)	..
Dog 1	21–36	20	25–36	..
Dog 3	11–16	12	13	..
Dog 4	10	18	12–31	..
Dog 5	22	44	53 right, 18 left	33
Dog 6	..	..	38	..
Dog 7	..	..	55	..

Blood-flow is measured in ml. per 100 ml. tissue per min.

removed from each of two dogs with no signs of osteo-arthropathy.

Unilateral transthoracic vagotomy in dog 2 was followed by disappearance of tenderness and reduction of heat and swelling of the limbs. This dog had bilateral lung metastases, but the lesions were more extensive on the side which was vagotomised. Because the peripheral blood-flow was not measured it was impossible to ascertain at which stage during operation the diminution occurred.

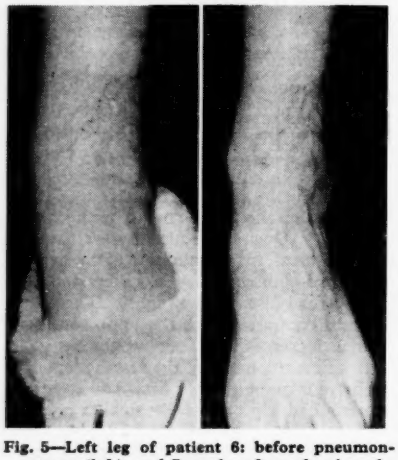

Fig. 5—Left leg of patient 6: before pneumonectomy (left), and 7 weeks after, showing the reduction of soft-tissue swelling (right).

The photographs were taken at the same distance and with the same magnification.

After dog 6 had been lightly anæsthetised with sodium pentobarbitone, atropine (1 mg. per kg.) was given intravenously. The onset of tachycardia and slowing of respiration indicated that the dose was sufficient to block vagal motor impulses, but the hyperæmia of the limbs was unaffected. This dog had bilateral metastatic lung lesions, and 2 days later bilateral cervical vagotomy was done. The limb blood-flow was unaffected by section of one vagus nerve, but it decreased promptly after bilateral vagotomy, though the cardiac output and blood-pressure were unaltered (fig. 8).

Increased blood-flow in the affected parts of the limbs was greatly reduced by adrenaline given intra-arterially (fig. 9), or by iontophoresis (table III).

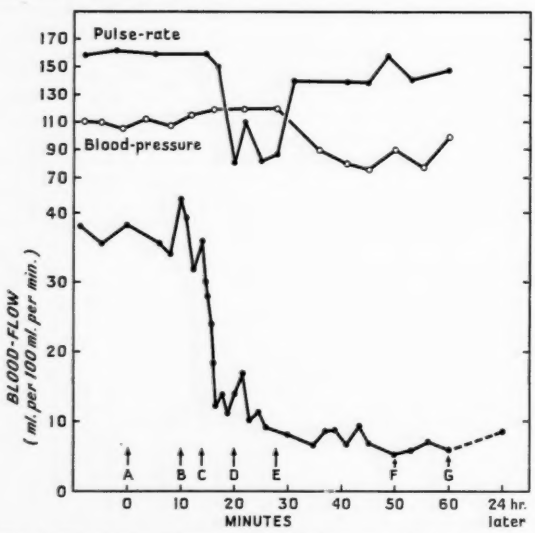

Fig. 6—Blood-flow, pulse-rate, and blood-pressure during and after left intrathoracic vagotomy (dog 5).

The hyperæmia lessened as the periosteum of the 4th rib was being dissected. (A) anæsthesia; (B) skin incision; (C) dissection of rib periosteum; (D) pleura opened; (E) left vagus cut; (F) chest closed; and (G) lungs reinflated.

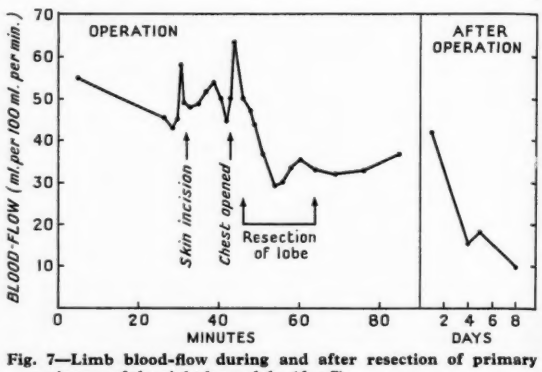

Fig. 7—Limb blood-flow during and after resection of primary carcinoma of the right lower lobe (dog 7).

The record shows halving of the blood-flow on resection of the affected lobe, and subsequent slower diminution of the hyperæmia.

Cross-circulation for 90 minutes between the limbs of an affected dog and a normal dog did not significantly affect the blood-flow in either (fig. 9).

The blood-gas studies in one patient and two dogs indicated no significant venoarterial shunt in the pulmonary circulation (table IV).

In single preliminary experiments, neither unilateral lumbar sympathectomy nor intra-arterial injection of the sympatholytic abent, bretylium tosylate, reduced the rate of blood-flow through the affected limb.

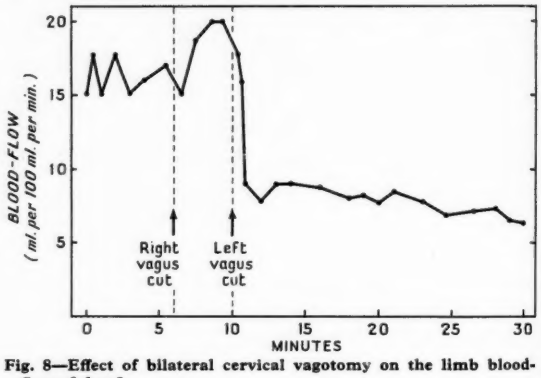

Fig. 8—Effect of bilateral cervical vagotomy on the limb blood-flow of dog 6.

Discussion

The primary anatomical change in the limbs of patients with osteoarthropathy seems to be the overgrowth of vascular connective tissue. In both man and the dog this change preceded the formation of subperiosteal new bone. During regression after operation, resolution of the soft-tissue changes was prompt; but diminution of the radiographic changes in bone became apparent only after 7 weeks in patient 5, and after 5 weeks to 4 months in the dogs (Brodey and Wind 1957, Rex 1959). New bone may form in the soft tissues apart from the periosteum, as seen in fig. 1; this has also been described in man by Gall et al. (1951) and in the dog by Holmes and Price (1958).

Increased blood-flow is closely associated with the overgrowth of connective tissue. Ginsburg (1958) found the blood-flow increased in the forearm or calf of fourteen of her eighteen patients with osteoarthropathy, and in the other four the blood-flow was no greater than in the control group. We found increased blood-flow in all our patients' limbs, though in patients 3 and 4 (table II) the increase was confined to the ankle where there was

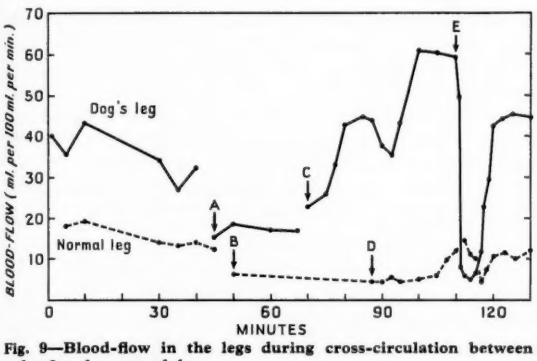

Fig. 9—Blood-flow in the legs during cross-circulation between dog 6 and a normal dog.

(A) Femoral vessels of dog 6 ligated; (B) vessels of normal limb ligated; (C) circulation of the normal dog perfused the limb of dog 6; (D) circulation of dog 6 perfused the normal limb; and (E) intra-arterial injection of adrenaline into the limb with osteoarthropathy.

prominent soft-tissue swelling. The degree of periosteal new-bone formation did not seem to be related to the increase of blood-flow in the surrounding tissues.

The negative results of our cross-circulation study weigh against the humoral theory of osteoarthropathy. The failure to find significant shunting of blood across the pulmonary circulation makes it unlikely that substances which bypass the pulmonary circulation are important in the ætiology of the condition.

The prompt regression of signs and symptoms of pulmonary osteoarthropathy after vagotomy (Flavell 1956) strongly favours a neurogenic element in the pathogenesis of osteoarthropathy. This is also supported by our finding, in bilateral pulmonary disease, that bilateral cervical vagotomy was associated with prompt reduction in limb blood-flow when unilateral vagotomy had proved ineffective (fig. 8); in this case (dog 6) cervical vagotomies were done to avoid the disturbances in peripheral blood-flow which might result from thoracotomy. Atropinisation, which paralysed only the motor fibres in the vagus, did not affect the hyperæmia; vagotomy therefore acts by interruption of the afferent fibres. Thus underlying pulmonary osteoarthropathy there seems to be a reflex of which afferent fibres travel in the vagus nerves.

According to this neurogenic theory, regression of osteoarthropathy after excision of the pulmonary lesion is attributable to removal of the locus of afferent impulses. When exploration of the thorax is beneficial, as in patient 2, the most likely reason is that afferent fibres of the vagus have been divided during dissection of the root of the lung. It is more difficult to explain the reduction of hyperæmia during incision or perforation of the chest wall, as in dog 5 (fig. 6). We do not know whether this change would last long because the dog was not permitted to survive operation; but the abruptness of the change suggests a neural mechanism. We suggest that, in such cases, the reflex had been affected by stimuli arising from trauma to the chest wall—a possibility which recalls the phenomenon of pleural shock.

Though certain measures are associated with prompt reduction in the hyperæmia of the limb, the increased blood-flow levels completely subsided only over the next few days (fig. 7, table III). The explanation most likely is that the wide vessels of the overgrown connective tissue passively admit an increased blood-flow until they undergo resolution.

The nature of the stimulus which causes osteoarthropathy has not been determined, nor has the efferent path of the reflex. The great sensitivity of the vessels to the constrictor effect of adrenaline (fig. 9, table III) suggests that the pathway is likely to be in the spinal sympathetic outflow tracts, but the negative results of lumbar sympathectomy or intra-arterial injection of a sympatholytic agent lend no support for this hypothesis. We plan further work in the hope that discovery of the efferent path of the supposed reflex may throw light on the innervation of the blood-supply to the connective tissues.

Summary

Pulmonary osteoarthropathy has been studied in man and in the dog. The manifestations in the two species are very similar, and the underlying mechanism seems to be the same.

The earliest anatomical change in the limbs was an overgrowth of highly vascular connective tissue, and this was followed by subperiosteal new-bone formation. Blood-flow increased in the affected areas; and differential studies suggest that the major part of the blood-flow was directed to the newly formed tissue.

Blood-gas measurements showed no significant veno-arterial shunt in the pulmonary circulation.

Cross-circulation between the limb of a normal dog and one with osteoarthropathy did not significantly affect blood-flow in either limb. This suggests that humoral factors are not implicated in the pathogenesis of osteoarthropathy.

Various procedures could cause regression of osteoarthropathy. This was associated with prompt reduction of the increased blood-flow, and followed by resolution of the soft-tissue overgrowth, and some weeks later there was regression of the bony changes.

In man regression of osteoarthropathy has followed removal of the primary lung lesion, exploratory thoracotomy, or unilateral vagotomy. Closer study of the

TABLE IV—ARTERIAL BLOOD-GAS STUDIES IN OSTEOARTHROPATHY

Subject	Breathing air				Breathing 100% oxygen				
	Oxygen tension (mm. Hg)				Oxygen tension (mm. Hg)				
Patient 4	Inspired air		Arterial blood		Inspired air		Arterial blood		
	149		71		673*		641*		
	Carbon dioxide (mm. Hg)	Oxygen			Carbon dioxide (mm. Hg)	Oxygen			
		Content (ml. per 100 ml.)	Capacity (ml. per 100 ml.)	Saturation		Content (ml. per 100 ml.)	Capacity (ml. per 100 ml.)	Saturation	Physically dissoved (ml. per 100 ml.)
Dog 2	34	14·8	15·9	91%	36	16·9	15·8	100%	1·1
Dog 3	29	15·9	17·8	87%	49	18·7	17·8	100%	0·9

* Calculated v-A shunt = 2·2% (normal).

manipulations leading to reduction of the limb blood-flow was possible in the dogs:

In two dogs the blood-flow lessened as the chest wall was incised, and in another it was not reduced until the pedicle of the affected lobe of the lung was severed.

In one dog unilateral intrathoracic vagotomy was followed by regression of osteoarthropathy. In another, with bilateral lung metastases, unilateral cervical vagotomy was not associated with changes in blood-flow, but bilateral vagotomy produced a prompt decrease. Previous atropinisation of this dog had not affected the limb blood-flow.

The reduction of increased blood-flow in the limbs by vagotomy, but not by atropinisation, suggests that the flow is maintained by a reflex with afferent fibres in the vagus nerves.

The efferent pathway of this reflex is undetermined. The sensitivity of the affected limb vessels to the vasoconstrictor effects of adrenaline suggests that the efferent path is via the spinal sympathetic outflow. But in single experiments neither lumbar sympathectomy nor intra-arterial injection of bretylium tosylate affected the rate of blood-flow in the limbs.

We are grateful to Dr. Brooke Roberts for carrying out the cross-circulation study; to Dr. William Hardesty for performing the lumbar sympathectomy; and to Dr. Robert Forster and Dr. George Polgar for the arterial blood-gas studies. We thank Burroughs Wellcome & Co. (Tuckahoe, New York) for a supply of bretylium tosylate.

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INCREASED ŒSTROGEN EXCRETION IN HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

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OCCASIONAL gynæcomastia was first noted in patients with hypertrophic pulmonary osteoarthropathy by Bamberger (1891), who compared the swelling of the breast observed in three men with pulmonary arthropathy with the mammary enlargement sometimes found in youths at puberty. Later, other workers commented on the association of gynæcomastia with arthropathy in patients with carcinoma of the bronchus (Fried 1943, Bloom 1948, Bariety and Coury 1950).

In a previous study of hypertrophic osteoarthropathy, œstrogen excretion was measured in three patients: urinary œstrogens were increased in all of them, though only one had gynæcomastia (Ginsburg 1958). We have therefore undertaken a more detailed study of œstrogen excretion in hypertrophic osteoarthropathy. Control observations have been made in patients with carcinoma of the bronchus uncomplicated by periostitis. Œstrogen excretion has also been measured in patients with clubbing of the fingers or gynæcomastia not associated with osteoarthropathy, and in a group of healthy men.

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The Investigation

Patients with Hypertrophic Pulmonary Osteoarthropathy

Studies were made in eleven men with pulmonary arthropathy (table I). They all had clubbing of the fingers, swollen joints, and radiographic evidence of periostitis. The osteoarthropathy was secondary to carcinoma of the bronchus in all except one (case 10) in whom the presumptive diagnosis was bronchiectasis. Two (cases 1 and 4) had gynæcomastia.

In all these patients urinary œstrogens were measured before operation on 2 consecutive days, and in five (cases 5, 7, 8, 10, and 11) for 6 days after the intramuscular injection of œstradiol 2·5 mg. in olive oil. In six of them (cases 2, 3, 5, and 7–9) œstrogen excretion was also studied after removal of the primary pulmonary tumour.

Control Groups (table II)

A. *Patients with carcinoma of the bronchus but without arthropathy.*—This group comprised six men and one woman. Two of the men (cases 16 and 18) and the woman (case 17) had clubbing of the fingers, but none of the patients in this group had radiographic evidence of periostitis. Urinary œstrogens were measured on 2 consecutive days before thoracotomy.

B. *Miscellaneous patients.*—The five men in this group included one with idiopathic clubbing of the fingers, one with clubbing secondary to steatorrhœa, and three with gynæcomastia. The gynæcomastia was associated in two cases with pulmonary tuberculosis, and in the third with carcinomatosis.

C. *Normal men.*—Urinary œstrogen output was determined in twenty-four healthy men whose ages ranged from 18 to 55. Generally at least two 24-hour specimens of urine were collected from each.

Methods

24-hour collections of urine from the patients were stored without preservative at 4°C, suitably packed, and despatched, from London to Edinburgh. The urinary excretion of œstriol, œstradiol, and œstrone were measured by Brown's method (1955b), as modified by Brown et al. (1957). Urine specimens from the healthy subjects were collected in Edinburgh.

Results

Urinary Œstrogen Excretion in Osteoarthropathy

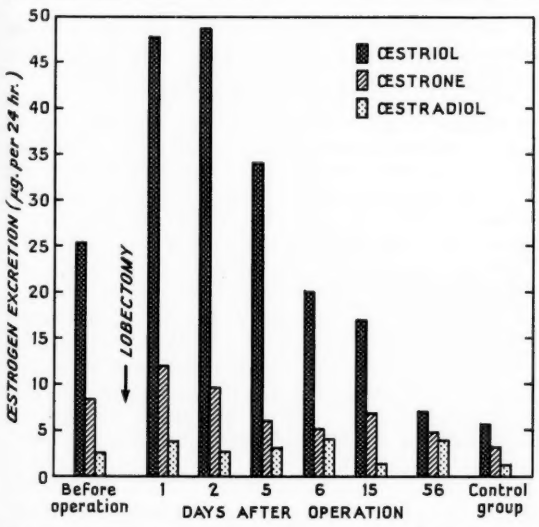
Of the eleven patients with hypertrophic pulmonary osteoarthropathy, eight excreted more œstriol than any of the normal men, three excreted more œstrone, six excreted more œstradiol, and seven excreted more " total œstrogens " (tables I and II). The highest " total œstrogen value " (case 3) was almost five times the normal mean.

When the mean values for the two groups as a whole were compared, the following differences were found:

	t	P
Œstriol ..	5·79	<0·01
Œstrone	0·92	>0·3
Œstradiol	3·19	<0·01
Total œstrogens	5·85	<0·01

The increases were therefore greatest in respect of the œstriol fraction, and this was reflected in the total œstrogens.

In the six patients 4–8 weeks after the primary pulmonary tumour had been removed, œstrogen excretion was consistently decreased to less than half the preoperation levels, and in all cases the values had returned to normal limits. In one patient (case 8; see figure), where measurements were also made



Urinary œstrogens in case 8 before removal of the primary tumour and after operation.

during the 1st week after operation, excretion of the three œstrogens was even greater in the immediate postoperative period, and it fell only gradually over subsequent weeks.

The recovery of injected œstradiol as the three urinary œstrogens (uncorrected for methodological losses) ranged from 7·5 to 22·3% (mean 14·7%), of which 31–85% (mean 55%) was œstriol (table III). These values compare with a range of 9 to 23% (mean 16%) for the normal, of which 27–59% (mean 44%) was œstriol (Brown 1957). The recovery figures are therefore normal, except that the œstriol fraction contributes a greater proportion of the urinary œstrogens, particularly when the endogenous output is high.

TABLE III—RECOVERY OF ADMINISTERED ŒSTRADIOL IN CASES OF HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

Case no.	Total * œstrogens recovered (% of dose)	Œstriol recovered (as % of total * recovered)
5	22·3	70
7	10·1	85
8	19·2	43
10	7·5	45
11	14·4	31
Mean ..	14·7	55

* Total refers to the sum of œstriol, œstrone, and œstradiol.

Urinary Œstrogen Excretion in Carcinoma of Bronchus Uncomplicated by Osteoarthropathy

In none of these patients was the excretion of urinary œstrogens greater than normal (table II); in fact, in five of them the œstrone values were below the normal range, and therefore œstriol again tended to be the major œstrogen. When the means of this group were compared with those of the group with osteoarthropathy, significant differences were found in all three œstrogen fractions:

	t	P
Œstriol ..	3·07	<0·01
Œstrone ..	3·26	<0·01
Œstradiol ..	1·96	<0·05
Total œstrogens	3·44	<0·01

Urinary Œstrogen Excretion in the Miscellaneous Group

In three patients (cases 19–21) with clubbing but without hypertrophic pulmonary osteoarthropathy, and in two patients (cases 21 and 22) with gynæcomastia, the œstrogen output was

TABLE I—ŒSTROGEN EXCRETION (μg. PER 24 HR.) IN HYPERTROPHIC PULMONARY ŒSTEOARTHROPATHY

Case no.	Age (yr.)	Extent of periostitis	Gynæcomastia	Œstriol	Œstrone	Œstradiol	Total urinary œstrogens
1	67	Gross changes in upper and lower limbs	+	27·0	9·0	3·2	39·2
2	57	Severe in legs, moderate in arms	−	13·3 (*5·7*)*	3·6 (*3·4*)	1·2 (*0*)	18·1 (*9·1*)
3	62	Severe in lower legs, slight in forearms	−	39·1 (*7·3*)	9·0 (*4·1*)	3·8 (*0*)	51·9 (*11·4*)
4	54	Severe changes in legs and forearms	+	17·6	6·4	2·9	26·9
5	53	Severe changes in legs and forearms	−	25·5 (*7·1*)	8·4 (*4·7*)	3·5 (*3·7*)	37·4 (*15·5*)
6	49	Moderate changes in lower legs, slight in forearms ..	−	11·9	6·0	7·7	25·6
7	47	Severe changes in legs, moderate in forearms ..	−	27·5 (*6·3*)	3·5 (*3·4*)	2·0 (*1·9*)	33·0 (*11·6*)
8	32	Moderate changes in legs and forearms	−	14·6 (*5·1*)	4·8 (*2·7*)	4·2 (*0·6*)	23·6 (*8·4*)
9	56	Moderate changes in legs only	−	9·7 (*4·3*)	2·9 (*0·6*)	0·8 (*0·9*)	13·4 (*5·8*)
10	50	Moderate changes in lower legs only	−	5·9	2·5	0·9	9·3
11	69	Slight changes in legs and forearms	−	5·1	5·9	0·4	11·4
		Mean value		17·9	5·6	2·8	26·3

* Figures in parentheses are postoperative values.

TABLE II—ŒSTROGEN EXCRETION (μg. PER 24 HR.) IN THE CONTROL GROUPS

Case no.	Age (yr.)	Special features	Œstriol	Œstrone	Œstradiol	Total urinary œstrogens
Group A:						
12	45	No finger-clubbing	6·3	4·9	2·3	13·5
13	61		6·7	1·6	0·4	8·7
14	53		9·5	2·4	0·9	12·8
15	63		5·4	1·7	0·6	7·7
16	61	Finger-clubbing	3·2	3·1	1·2	7·5
17	61		4·0	1·0	0·3	5·3
18	69		4·3	2·3	2·8	9·4
		Mean value	5·6	2·4	1·2	9·2
Group B:						
19	25	Idiopathic clubbing	4·7	6·0	1·7	12·4
20	72	Clubbing secondary to mild steatorrhœa	5·4	1·9	0·7	8·0
21	58	Bilateral gynæcomastia; slight clubbing; pulmonary tuberculosis	6·2	3·6	0·3	10·1
22	65	Right gynæcomastia; no clubbing; pulmonary tuberculosis ..	3·7	5·4	1·3	10·4
23	53	Bilateral gynæcomastia; no clubbing; mediastinal tumour with cervical gland involvement	30·1	5·3	3·0	38·4
Group C:	normal men					
	Actual range		1·9 to 11·1	2·8 to 7·9	0 to 2·8	7·2 to 19·6
	Mean ± S.D.		4·7 ± 2·7	5·1 ± 1·4	1·3 ± 0·7	11·1 ± 3·1

Group A = carcinoma of bronchus uncomplicated by osteoarthropathy.
Group B = miscellaneous cases. Group C = normal men.

within the normal range. But in one (case 23) with a complex picture of gynæcomastia associated with a mediastinal tumour and glandular involvement, the œstriol output was much greater than normal.

Discussion

In the group of healthy men the urinary excretion of œstriol, œstrone, and œstradiol agrees closely with that already reported (e.g., Brown 1955a, Bersohn and Oelofse 1957). In the majority of the patients with hypertrophic pulmonary osteoathropathy the excretion was greater than that in any of the normal men, the greatest difference being in the œstriol values. In patients with arthropathy there was no precise correlation between severity of symptoms or extent of radiographic changes and the level of œstrogen excretion; but the urinary œstrogen levels tended to be higher in patients with marked periostitis than in those with only slight radiographic changes.

In the group of patients with bronchial carcinoma uncomplicated by arthropathy but accompanied in some instances by finger-clubbing, the excretion of œstrogens was not increased. This was also found in patients with gross clubbing due to other causes. The high level of urinary œstrogens observed in the patients with pulmonary arthropathy was not therefore a universal feature bronchial carcinoma nor associated with severe clubbing, but it was apparently related to periostitis of the long bones.

In the patients with osteoarthropathy, the proportion of injected œstradiol recovered as the three urinary œstrogens was within normal limits, although, as with the endogenous output, proportionately more tended to be excreted as œstriol. This indicates that conjugation and inactivation of œstrogens was unimpaired—at least in so far as the pathway to œstriol is concerned—and that the increased levels of urinary œstrogens found in osteoarthropathy reflect increased hormonal production. The source of this excessive œstrogen production is not readily apparent. The pulmonary tumour can be excluded as a source, because joint pain and swelling were relieved immediately after operation, although the urinary œstrogens remained high in the early postoperative period (case 8; see figure) and only fell to normal values some 3–4 weeks later. Moreover, in case 7, 3 months after pneumonectomy, when there were multiple deposits including pulmonary secondaries, œstrogen excretion was less than a third of the preoperative value.

High levels of urinary œstrogens are rare in men. They may be associated with feminising testicular tumours, but there was no evidence of such a tumour in any of the patients with osteoarthropathy. The observed increase could result from increased production in the adrenals; this possibility has not been fully investigated because exhaustive tests of adrenal activity were not performed. In five patients (cases 4, 8, and 9–11) the urinary 17-ketosteroids and 17-ketogenic steroids were measured, and found to be normal (range 4·5–11·6 mg., mean 6·8 mg.; and range 4·0–11·4 mg., mean 8·1 mg., respectively), though only two of these patients were excreting increased amounts of œstrogens. In support of these findings, however, Bariety et al. (1960) reported low or normal levels of urinary 17-ketosteroids in twenty-four patients with hypertrophic pulmonary osteoarthropathy.

The output of urinary œstrogens may sometimes be increased in liver disease. Thus, Cameron (1957a and b) found raised values in two of twelve patients with chronic liver disease, the " total œstrogens " excreted being 42 and 35 μg. per day; the output of all three œstrogens was increased in one of these, and in the other œstriol only increased. Cameron also observed that the proportion of œstriol to total œstrogens tended to be higher than normal in patients with liver disease, as it was in our series, but such a ratio seems to be common to a number of unrelated disorders (Brown 1960). Possibly therefore the increased œstrogen production found in arthropathy is related to hepatic dysfunction—for example, to a disturbed metabolism of œstrogen precursors such as testosterone. However, in none of our patients was there any clinical or simple biochemical evidence of liver disease.

Although the initial impetus for our study was the onset of gynæcomastia in men with osteoarthropathy, this was not found invariably, and no correlation was subsequently observed between the presence of gynæcomastia and the urinary œstrogen level. Thus, two patients with arthopathy (cases 3 and 5) had no feminising signs, although œstrogen excretion was high, yet another patient (case 1), with a similar urinary œstrogen level had considerable breast changes; and, conversely, in two men with gynæcomastia not associated with carcinoma (cases 21 and 22) œstrogen excretion was within the normal range. These findings support the view that feminising changes in the male are not simply related to œstrogen production but may depend on other factors (Kark et al. 1951, Brown 1960).

The finding of one patient (case 23) without arthropathy but with gynæcomastia, a mediastinal metastasising tumour, and an increased œstrogen output, suggests that among such cases others might have an abnormal œstrogen pattern not necessarily associated with osteoarthropathy. Further studies of metabolic changes in these cases, and in men with osteoarthropathy, may not only reveal the origin of the excess œstrogens but also throw light on the control of the normal male balance between œstrogens and other hormones.

Summary

Urinary excretion of œstriol, œstrone, and œstradiol was measured in eleven men with hypertrophic pulmonary osteoarthropathy, in a control group of seven patients with carcinoma of the bronchus uncomplicated by arthropathy, in five patients with clubbing of the fingers or gynæcomastia associated with other diseases, and in twenty-four healthy men.

In patients with pulmonary arthropathy the mean œstrogen excretion was more than twice that of the control group or of the healthy men, and it fell to within normal limits some weeks after operation. Recovery of injected œstradiol was within normal limits.

No relation was found between the presence of gynæcomastia and the level of urinary œstrogens.

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PARTIAL PITUITARY ABLATION

By Needle Implantation of Gold-198 Seeds for Acromegaly and Cushing's Disease

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HITHERTO, in the treatment of hyperpituitary states the only serious alternative to standard external radiotherapy has been surgical operation—either on a peripheral gland as in Cushing's disease treated by partial or total adrenalectomy (Sprague et al. 1961), or on the pituitary gland itself, as in severe acromegaly (e.g., Henderson 1939). Unfortunately in "successful" pituitary surgery, pituitary hyperfunction is usually supplanted by hypofunction, and removal of the pituitary disease is often incomplete; moreover the operation exposes to hazard the vital adjacent structures. In standard radiotherapy to the pituitary, an upper limit of radiation has to be set because the optic and occulomotor nerves perforce receive approximately the full radiation applied to the gland. Since exposure of these sensitive nerves to more than 8000–10,000 rads involves some risk of damaging them (Kelly et al. 1951, Buys and Kerns 1957), external irradiation of the pituitary is usually kept under the maxima of 4000 rads per course and 8000 rads total radiation. Yet even within these limits radiotherapy for hyperpituitary states has proved beneficial, often giving useful palliation in acromegaly (e.g., Johnsen 1952), and in a small proportion of cases of Cushing's disease even yielding apparent cure (Dohan et al. 1957). Clearly more intensive radiotherapy, if equally safe, might play an important part in the treatment of these diseases.

Experience has already shown that for the treatment of thyrotoxicosis external radiotherapy is inadequate, because safe deep-X-ray therapy gives insufficient radiation; but radio-iodine can deliver larger doses safely and effectively from within the gland, usually without destroying thyroid function. Equivalent effects should be attainable equally safely in the pituitary by needle implantation of appropriate radioisotopes within the gland. It has already been found that well-placed needle implants of yttrium-90, whose radiations are very localised, can deliver over 100,000 rads to the whole gland and so achieve its ablation without damaging the optic nerve (Fraser et al. 1959). Less intense radiation similarly localised within the gland should be obtainable with implants of gold-198, and might arrest the disease without impairing normal pituitary function—an objective comparable with that usually attained in the treatment of thyrotoxicosis with radio-iodine. We report here our preliminary results in 18 patients with acromegaly and in 6 patients with Cushing's disease in whom gold-198 was implanted by needle to effect partial pituitary ablation—i.e., arrest of the hyperfunctioning state along with preservation of normal pituitary function.

Choice of Gold-198

Yttrium-90 has already been found the most suitable isotope for complete pituitary ablation, since its intense, but highly localised, radiation can deliver 100,000 or more rads to the whole gland, while about 4 mm. beyond the gland periphery the dose delivered does not exceed 8000–10,000 rads.

For partial pituitary ablation, the implantation should deliver as evenly as possible throughout the whole gland a dosage intermediate between this necrotising dosage of 100,000 rads and the 8000 rads maximum attainable with external radiotherapy—i.e., probably in the range 15,000–40,000 rads—and also give less than 10,000 rads to the nearest nerve tissue, the optic nerves. To attain this moderate dosage fairly uniformly throughout the pituitary gland, ^{198}Au, a medium γ-emitter, provides a better source than Y-90, a pure β-emitter, as can be seen from fig. 1. An ideally placed implantation of ^{198}Au designed to give a dose of not more than 10,000 rads to the diaphragm will give an average dose of about 25,000 rads to the gland as a whole. (In estimating this value the small volume of gland contained within 1 mm. around each grain has been excluded, since it receives an extremely high dose.) At 2·5 mm. beyond the gland surface receiving 10,000 rads, only 4000 rads will be given (fig. 1). A similarly planned implant of radon, a hard γ-emitter (of effectively 1·65 and 0·55 Mev. as against 0·411 for ^{198}Au) might attain an equivalent result in the gland, but would be less desirable since its dosage beyond the gland would fall off slightly more slowly.

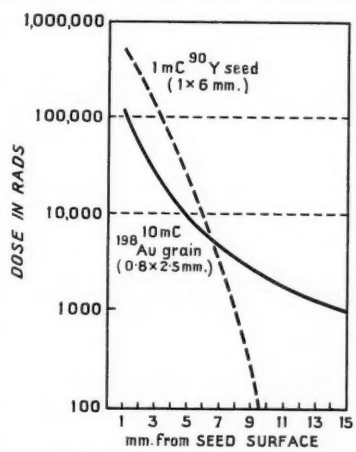

Fig. 1—Comparison of depth-dose curves for ^{198}Au and ^{90}Y.

Methods

Planning the Implant

The gland dimensions are first estimated as accurately as possible. In the cases without pituitary tumour this can be done with reasonable accuracy by the measurement of skull films taken in the lateral and 25° tilt fronto-occipital projections, using the landmarks previously defined (Bloch and Joplin 1959). In the cases with a radiologically demonstrable pituitary tumour (17 out of 18 acromegalics) lateral tomograms are needed to show the fossa shape, which often differs in various sagital planes, and an air-encephalogram is needed to indicate the presence of upward extension. As air-encephalography rarely gives a clear definition of the upper surface of the tumour, the implant is usually planned assuming for safety that the upper surface is in its normal radiological position. When the gland shape and size have been worked out, the number, position, and desired irradiation intensity of the seeds are calculated so that the dose reaching the gland surface is 10,000 rads, when the seeds are implanted on either side of the midline.

Implant Technique

No steroid cover was used for this series, but routine cover with sulphadiazine and streptomycin was given for one preoperative day and five days postoperatively. After anæsthesia and intubation the patient's head is gripped by rubber-padded side-plates of 'Perspex', which are fixed to the table-top. A 5 in. image-intensifier mounted on a movable arm enables the pituitary area to be screened in both lateral and occipitofrontal

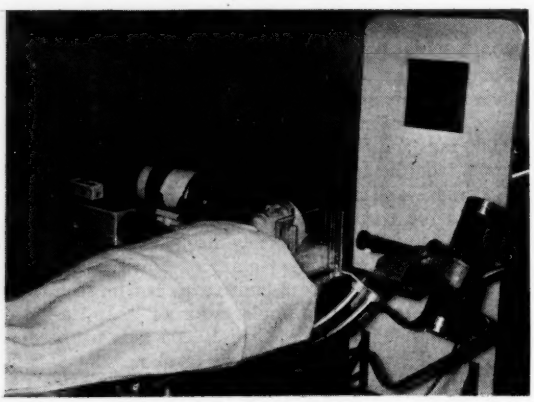

Fig. 2—Arrangement of image-intensifier for screening during implantation.

planes (fig. 2). Irradiation dosage is minimised by the use of the image-intensifier, and a beam coned down to a 2 in. diameter. Screening is done at 0·5 to 2·0 mA and 75 to 85 Kv.

The implantation technique is as follows:

The operator drills a small hole through the nasal bone 5–10 mm. from the midline. A trocar and canula are passed, under screening control, as far as the anterior wall of the pituitary fossa. Then, while the canula is kept in the same position, the trocar is removed and replaced by a drill, with which the anterior wall of the fossa is perforated after X-rays have confirmed the correct position. The drill is then withdrawn, and an end-delivery needle is passed down the canula into the gland, through which a seed is pushed by a stilette. Several seeds can be implanted at the required distances from the anterior wall of the fossa. A similar procedure is carried out on the other side.

Following the implant X-rays are taken, in the same projections as before the implantation, to show the position of the seeds in order to estimate the irradiation dose.

Assessment of Results

During a pre-implant hospital admission each patient was carefully assessed so that only undoubted cases were treated in this trial of the method. Subsequently, about three months after the implant, 16 out of 18 of the acromegalic patients were again admitted for similar assessments; and thereafter regular assessments have been made, both at outpatient attendances and also as indicated during inpatient admissions. Follow-up observations have been made for from three to nineteen months in the 16 acromegalic patients, and for from eight to twenty-four months in 5 of the 6 patients with Cushing's disease.

To supplement the regular clinical examinations, special methods were used for serial appraisal of the activity of the disease in these patients. For the acromegalic patients these included hand-volume measurements, an augmented intravenous insulin-tolerance test using 11·1 units per sq. m. body-surface (Harrison et al. 1960), and a prednisone glycosuria test for prediabetes (Joplin et al. 1961). The insulin-tolerance test reveals insulin resistance—a characteristic of active acromegaly—by a rapid return of the blood-sugar to fasting levels (which is indexed by the sum of the 60, 90, and 120 minute blood-sugar values, a normal index being under 145 mg. per 100 ml.). The prednisone glycosuria test reveals a pre-diabetic abnormality in most active or untreated acromegalic patients with normal glucose-tolerance tests (Joplin et al. 1961). For the patients with Cushing's disease the special tests were urinary steroid measurements—17-ketogenic steroids basally and after dexamethasone suppression tests (Slater et al. 1961) in most, and in some measurements of the 24-hour urinary cortisol excretion and of the cortisol-production rate, using ^{14}C-cortisol. The last two of these measurements were kindly made by Dr. C. L. Cope (Cope and Black 1958, 1959).

Fig. 3—Patient (*a*) before and (*b*) after ^{198}Au implantation for acromegaly.

Patients Treated

Acromegaly

The 18 patients treated by ^{198}Au implantation comprised 8 males and 10 females aged 30–62 (mean 45). Previously 7 had been treated by external irradiation, with doses of 4000–8000 rads, given in one to three courses, but without any regression of the acromegalic facies and with only a few months' relief of headache or paræsthesiæ in the 3 patients in whom such symptoms were relieved. In 4 cases typical diabetes mellitus was present, while in a further case manifest diabetes had previously been present. Besides acromegaly, 2 patients had Graves' disease, and another had malignant hypertension.

TABLE I—EFFECTS OBSERVED FOLLOWING IMPLANTATION OF ^{198}AU IN ACROMEGALY

Observations	No. of patients
Clinical:	
Facies changed	6/16
Hand-volume (50 m. +) loss	1/15
Paræsthesiæ lost	5/8
Headache lost or much less	9/10
Eyes—field loss before or after implant.	0/18
Hormone-dependency induced (cortisone and thyroid)	1/17
Tests:	
Prediabetes or diabetes lost	4/7
Diabetes much improved	1/1
Insulin-tolerance test "normalised"	6/11
Change in pituitary fossa size and shape	0/18

All 18 patients showed obvious clinical acromegaly, and enlargement of the sella turcica was present on X-ray in 17. 8 had paræsthesiæ and 9 had headaches. Metabolic abnormalities characteristic of acromegaly were shown: (*a*) in 11 out of 12 patients tested for insulin resistance by the augmented intravenous insulin-tolerance test (see fig. 4), rapid recovery from insulin hypoglycæmia was found (i.e., the sum of their 60, 90, and 120 minute blood-sugar levels, after 11·1 units of soluble insulin per sq. m. of body-surface, was over 145 mg. per 100 ml.); and (*b*) in 7 out of 8 with normal glucose-tolerance tests evidence of pre-diabetes emerged on the prednisone glycosuria test (Joplin et al. 1961).

Cushing's Disease

The 6 treated cases (2 in males and 4 in females, aged 11–60) were clinically all clear-cut. In 5 cases the diagnosis was confirmed by finding basal urinary 17-ketogenic steroids raised above 20 mg. per twenty-four hours, and in all 6 cases by finding incomplete suppression of urinary 17-ketogenic steroids on 2 or 4 mg. of dexamethazone daily or 10 mg. of fluorocortisol daily for seven days. Cortisol-production rates, estimated with ^{14}C-cortisol by the kindness of Dr. Cope, were raised in the 4 cases tested. All these cases were considered to have adrenal hyperplasia rather than an adenoma. This was based on the finding that (*a*) tomograms following presacral insufflation of oxygen failed to show either a tumour or unilateral adrenal atrophy, and (*b*) a dexamethasone suppression test showed some, though incomplete, suppression of urinary

TABLE II—URINARY STEROID MEASUREMENTS IN 3 CASES OF CUSHING'S DISEASE BEFORE AND AFTER ^{198}AU IMPLANTATION

Age (yr.)	Sex	Relation to implantation	Urinary steroids (mg. per 24 hr.)					
			17-Ketogenic steroids (17-K.G.S.) and 17-ketosteroids (17-K.S.)				Cortisol	
			Basal		After dexamethasone*			
			17-KGS	17-K.S.	17-K.G.S.	17-K.S.	Urinary excretion	Production-rate (by ^{14}C)
25	F	Pre-implant.	45	26	13	16 *b	1·870	95
		3 mos. post-implant.	8	5	0	2 *s	..	9
		21 mos. „ „	8	4	1	3 *s	..	..
11	F	Pre-implant.	14	11	..	..	0·212	45
		7 mos. post-implant.	11	6	4	5 *s	0·051	17
		11 mos. „ „	..	..	5	1 *s	..	..
		22 mos. „ „	7	7	5	5 *a	..	..
11	F	Pre-implant.	25	9	11	8 *a	0·305	58
		2 mos. implant.	4	2	..	..	..	..

* The standard dosage for this dexamethasone test was 0·5 mg. 6-hourly for 7 days with the two urine samples collected on the 6th and 7th days (Slater et al. 1961). Tests after standard dosage are marked *s*; others of adequately equivalent dosage are marked *a* for dexamethasone 1·0 mg. 6-hourly and *b* for fluorocortisol 10 mg. daily.
The normal response on any of these dosages is reduction of urinary 17-ketogenic steroids to below 2 mg. per day.

17-ketogenic steroids (table II). We now consider that a rapid clinical response to pituitary irradiation provides the essential confirmation of this as the final diagnosis. One of these cases, showing occulomotor paresis, was considered to have an invasive pituitary tumour and has been described previously (Joplin and Fraser 1961).

Results

Any changes observed are reported as a proportion of the total subjects assessed on the point in question.

Acromegaly

The main clinical and test changes are summarised in table I. Headaches and paræsthesiæ usually ceased (9 out of 10, and 5 out of 8). This symptomatic relief was often obtained in the first week, while the more resistant cases needed a second implant of yttrium to achieve it (see later). In 6 of 16 patients regression of the acromegalic facies was observable, though all remained clearly acromegalic. Only 1 of 15 showed measurable shrinkage in volume of both hands (i.e., over 50 ml.). Fig. 3 illustrates the change observed in a case previously reported (Harrison et al. 1960). In seven patients the skin was noticed to become less coarsely thickened and less greasy.

Tests of carbohydrate metabolism showed changes in most cases. Of the 3 diabetics who previously had required insulin, 1 not only reverted to a normal oral glucose-tolerance test but also to a normal prednisone glycosuriea test—i.e., she lost all evidence of pre-diabetes; the other 2 attained good clinical control either on diet alone or with reduced insulin dosage. Many of the non-diabetics on the insulin-tolerance test and/or on the prednisone glycosuria test reverted towards normal. Fig. 4 shows that on the insulin-tolerance test 6 out of 11 patients lost their insulin resistance after the implantation. Similarly in 4 out of 7 patients after the implantation the prednisone glycosuria test no longer indicated prediabetes but instead a normal result. Thus, in summary, nearly all lost their symptoms of paræsthesiæ or headaches, and showed some signs of remission in their acromegalic features, along with corresponding metabolic changes, most clearly demonstrated by improvement in their carbohydrate metabolism indicating lessened insulin resistance.

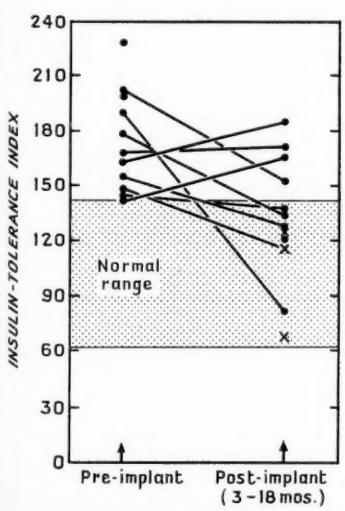

Fig. 4—Insulin-tolerance test results before and after ^{198}Au implantation in 11 acromegalic patients.

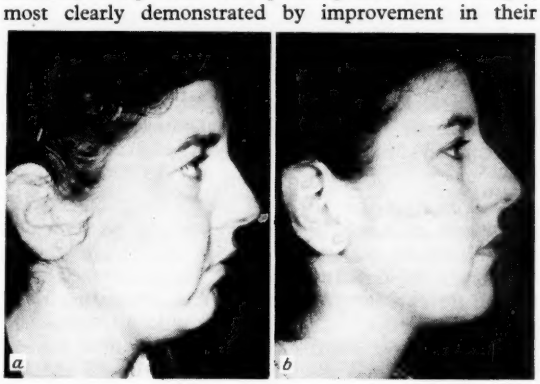

Fig. 5—Patient (*a*) before and (*b*) after ^{198}Au implantation for Cushing's disease.

Cushing's Disease

In all of the 6 patients one or more full postoperative assessments have been made. In the 1st patient a clearly full remission (see fig. 5) and in the next 2 patients (children) a striking and probably complete remission has been attained. In the 4th case, where the disease was due to a malignant invasive pituitary tumour, very considerable remission has been attained (Joplin and Fraser 1961). The remaining 2 cases showed no improvement on follow-up.

The condition of the 4th case, due to the invasive pituitary tumour, has been further reassessed nine months after the implantation. He now has a normal output of 17-ketogenic steroids and he no longer shows the evidence of pre-diabetes which was present before the implantation. His clinical appearance is one of remitted Cushing's disease, and the preoperative right 3rd cranial nerve palsy has now recovered.

The first 3 cases—a girl of 11, a boy of 11, and a woman

of 23—have been followed up for ten, twenty-two, and twenty-four months respectively. The 2 children, who previously had gained no height during a year, are now growing at the normal rate for their age; and the boy is showing normal pubertal development. All have lost their mood disorder, weakness, striæ, bruising, hypertension, and hirsutism, and the boy has lost his bone pains. The urinary steroid excretion has returned to normal. The changes observed in their test data are summarised in table II.

Complications

There was no cerebrospinal-fluid (C.S.F.) rhinorrhœa or cranial nerve damage in this series of 24 patients. Visual fields were plotted before and after implantation in every case and were always found normal. Diabetes insipidus developed in 1 case. None of the patients with Cushing's disease developed any complications. 4 of the acromegalic patients had postoperative signs suggestive of meningitis; C.S.F. was sterile, and accordingly the cause was probably infection in the pituitary. In 1 of these patients antibiotic treatment was delayed owing to misdiagnosis; and generalised meningitis developed from which she ultimately died. In the other 3 these signs settled in a few days on antibiotics; antibiotics were continued for several weeks, and no features of infection recurred

All but 3 of the patients were tested after implantation for evidence of thyroid and adrenal function by I^{131} and water-diuresis tests, as well as by urinary steroid measurements. Of the acromegalic patients who developed the syndrome suggesting pituitary abscess or infection, only 1 subsequently showed any signs of pituitary deficiency and required corticosteroid and thyroxine therapy.

Discussion

These findings show that pituitary overactivity causing acromegaly or Cushing's disease can be substantially reduced by implantation of seeds of ^{198}Au without inducing hypopituitarism, and that this can be done with little morbidity in the former and none in the latter disease. The results in these two conditions suggest that the radiation dose used is usually insufficient to correct acromegaly but may often suffice in Cushing's disease. This may be due either to the intrinsically greater radioresistance of cells secreting growth hormone than of those secreting corticotrophin, or to the greater difficulty in defining the exact outline of the adenomatous gland leading to underdosage. Pituitary infection after the implant was encountered only in the acromegalic series. This may have depended on the liability of adenomatous glands to contain areas of necrosis from an impaired blood-supply, which readily act as a nidus for infection. If a careful watch is kept for clinical evidence of meningitis so that antibiotics are given early, this involves little more disturbance to the patient than a moderate upper-respiratory infection.

It would seem that the dose-plan used in this study is well within the tolerance of the nearby cranial nerves, and of the diaphragma sellæ, in that no evidence of neurological damage or of C.S.F. rhinorrhœa was found. To date a total of 30 such ^{198}Au implants have been done for various disorders, using the dose-plan described here. These comprised, in addition to the cases described in this paper, 5 cases of severe exophthalmos and 1 case of pituitary tumour without endocrine disorder. In none of these additional cases was any such complication seen. These 5 cases of exophthalmos were treated in this way only when it had become apparent that they were deteriorating despite conventional therapy with bedrest, thyroxine, corticosteroids, and diuretics; of these, 4 showed a distinct reduction in the congestive features, but no significant improvement in ocular paresis.

In the acromegalics the results show that the dose used was a little too low. This is confirmed by the observation that of 5 cases which had shown insufficient clinical response to the ^{198}Au implantation 4 had clear remissions when subsequently ^{90}Y seeds were implanted. These gave a higher central dose while delivering only 10,000 rads to the gland surface. 2 of these cases became steroid- and thyroxine-dependent. In the light of these experiences, it is planned to treat the next series by implanting a combination of ^{198}Au and ^{90}Y as the primary procedure. Thus we hope to obtain both a diffuse γ irradiation penetrating into the irregular projections from the tumour surface and so ensuring at least some irradiation of the entire tumour without risk of damage to adjacent structures, and also an intense central dose which should destroy the major part of the tumour bulk. Some such cases might then be expected to become hormone-dependent.

The preliminary results in the Cushing's series are possibly more encouraging, and no modification of the procedure is yet planned. These rapid regressions strongly support the view that Cushing's disease, or Cushing's syndrome associated with bilateral adrenal hyperplasia, may depend on pituitary hyperfunction (Cushing 1932). Furthermore no lowering of normal adrenal function has been seen in exophthalmic subjects when they have been given the same pituitary irradiation dose.

A review of the previous reports of cases of acromegaly and Cushing's disease (Fraser and Joplin 1961) showed that hitherto external irradiation to the pituitary has achieved some definite results in both diseases, and in a very few cases full remission. Yet heavier radiation, using needle implantation of 90Y seeds, can achieve good results more often (e.g., Dogliotti et al. 1959, Molinatti et al. 1959). Our results give further encouragement to the development of this method of radiotherapy.

Summary

The results of needle implantation of seeds of ^{198}Au into the pituitary in 18 cases of acromegaly and 6 cases of Cushing's disease show that nearly all of the former had symptomatic relief and decrease in their signs of acromegaly, and 4 cases of Cushing's disease had a striking, if incomplete, remission.

Morbidity is confined to occasional infection in the tumour cases; this is readily treatable with antibiotics. Subsequent replacement therapy was not required except in an acromegalic who had developed pituitary infection.

It is a pleasure to acknowledge our indebtedness to our colleagues in England and overseas for referral of cases, to our colleagues in the department of chemical pathology who carried out many of the estimations reported, and to the Medical Research Council for the image-intensifier equipment.

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RESPIRATORY FAILURE DUE TO POLYMYOSITIS TREATED BY INTERMITTENT POSITIVE-PRESSURE RESPIRATION

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POLYMYOSITIS now ranks with myasthenia gravis and polyneuritis as a cause of pharyngeal palsy. A fatal outcome, due to bronchopneumonia, in a patient with subacute polymyositis was reported by Potain (1875). Since then pharyngeal or respiratory paralysis with associated bronchopneumonia has been recognised as the cause of death in a large proportion of fatal cases. We report here a case of polymyositis in which pharyngeal palsy and severe bronchopneumonia with respiratory failure developed and recovery followed intermittent positive-pressure respiration (I.P.P.R.).

Case-report

The patient was a 30-year-old married woman, with a healthy child aged 6 years. In May, 1960, she began to have pain and stiffness in several large joints. Treatment with phenylbutazone was followed by œdema of the face. She was admitted to the Law Hospital, Carluke, Lanarkshire, on June 1, 1960, with non-pitting œdema of the face and arms and pitting œdema around the ankles. She had pain in both hips and shoulders. The blood-pressure was 160/100 mm. Hg. Clinical examination revealed no other abnormality. The urine was normal. The hæmoglobin level was 83% and the white-blood-cell count 4000 per c.mm. The serum-albumin was reduced to 2·5 g. per 100 ml., and the serum-globulin was 3 g. per 100 ml.; the electrophoretic pattern of the serum-proteins was normal. Lupus erythematosus (L.E.) cell preparations were negative. Biopsy specimens of skin and muscle were normal. No definite diagnosis was made. The patient's condition improved steadily without treatment, and she was discharged from hospital on June 20, 1960.

When seen as an outpatient on July 8, 1960, the patient complained of dysphagia and was noticed to be dysarthric; in addition, she had pitting œdema of the legs and thighs. She was treated with methyl prednisolone 4 mg. t.i.d. and an oral diuretic (bendrofluazide 10 mg. daily) as an outpatient because she declined admission. Five days later there was demonstrable weakness of the palate and of all four limbs: the tendon reflexes were difficult to elicit. The œdema of the legs was less pronounced. The methyl prednisolone was increased to 8 mg. t.i.d. for a week and was then reduced to its former level.

Despite the evident deterioration in her condition, and against advice the patient travelled south on July 20, 1960, to take a holiday in East Anglia. At this time her voice was weak and her speech nasal. She had difficulty in swallowing and regurgitated fluids through her nose; she could eat and drink only very little. On July 27 she became suddenly breathless and was too weak to cough. Because of her evident respiratory distress and cyanosis she was admitted to Kettering General Hospital as an emergency.

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State on Admission

On examination the patient was cyanosed, with a temperature of 101·4°F and a pulse-rate of 160 per minute. There was a fusiform swelling around the right elbow-joint extending from the mid-arm to the mid-forearm; this pitted on pressure. There was no other œdema. Her respirations were rapid and shallow, and the air bubbled through a pool of secretions in her pharynx. There were widespread râles over both lung fields. The cardiac rhythm was regular, the blood-pressure was 140/70, and the jugular venous pressure was raised 2·5 cm. above the sternal angle. The heart was slightly enlarged to the left, and there was a presystolic apical gallop rhythm. Besides the pharyngeal palsy, there was weakness of the muscles of mastication and of both sides of the face, which had a "myopathic" appearance. There were early flexion contractures of the elbows, the hips, and the knees. There was generalised muscle wasting, which was greatest around the limb girdles and was accompanied by great weakness. The muscles were firm to the touch and tender on pressure. All tendon reflexes were absent, but the abdominal reflexes and plantar responses were normal. There was no sensory loss.

A chest X-ray showed no signs of pneumonia; the hæmoglobin was 100% and the white-blood-cell count 17,000 per c.mm. (polymorphs 88%). The cerebrospinal fluid (C.S.F.) was normal. The sputum contained a mixture or organisms, *Streptococcus viridans* predominating.

The patient was nursed in an oxygen tent but remained cyanosed. She was too weak to expectorate her tracheal secretions, and a tracheostomy was performed on the day of admission and a silver tube was inserted. After bronchial toilet her condition improved somewhat, but during the next three days signs of bilateral bronchopneumonia developed despite administration of 4 million units of penicillin daily. She was obviously still inhaling secretions. A cuffed rubber Radcliffe tracheostomy tube was inserted, and she was transferred to the respiration unit at the Churchill Hospital on July 30, 1960.

Further Investigations and Treatment

The patient's vital capacity was 400 ml. and her maximum breathing capacity only 6 litres per minute. Accordingly her respiration was assisted with I.P.P.R. from a Radcliffe respirator. She also received vigorous chest physiotherapy with postural drainage. At first she was given tetracycline (combined with oral and systemic nystatin because oral thrush had developed, and later chloramphenicol. She also received prednisolone 10 mg. t.i.d.

The results of other investigations were: C.S.F. normal; blood-urea 40 mg. per 100 ml.; urine grew *Escherichia coli* and proteus.

The artificial respiration was maintained continuously until Aug. 12, 1960, when the patient began periods of free breathing, which increased in duration until she dispensed with artificial respiration altogether on Sept. 2. During this time the bronchopneumonia gradually resolved, the thrush cleared completely, and the patient's general condition improved notably. The œdema around the right elbow disappeared; and the contractures of the elbows, hips, and knees were straightened. The wasting of the muscles did not progress, and their power slowly increased, so that she was able to walk on Sept. 1, although with a distinctly waddling gait. The tendon reflexes returned, and those in the legs were rather brisk. At this stage the vital capacity had increased to 1500 ml. and the maximum breathing capacity to 35 litres per minute.

Between July 30 and Sept. 2 the patient was fed through a tube passed through the nose into the stomach. She then became able to swallow fluids, and by Sept. 6 a soft diet, although examination of swallowing by cine radiography with barium showed the pharyngeal mechanism still to be grossly deranged.

Convalescence

The patient then began a lengthy convalesence, protracted by the continued dysphagia. Gradually it became possible to deflate the cuff of her tracheostomy tube between feeds, but it was not until the beginning of January, 1961, six months after the development of frank pharyngeal palsy, that her swallowing

returned to normal as judged by cine-radiographic recording of a barium swallow. The cuffed tube was then removed from her trachea and replaced by a silver tube for a few days. This was then removed. The tracheostomy did not close spontaneously, and a plastic closure was carried out on Jan. 27. At the time of her return home, the patient felt well, but still had myopathic facial weakness and considerable weakness of her pelvic girdle muscles.

Biopsy

In the early stages of the illness no diagnosis was made, but, as it evolved, the development of widespread muscular wasting and weakness with firm tender muscles raised the possibility of polymyositis. This diagnosis was clinched by biopsy of the left deltoid on Aug. 23, 1960. The report of the histological appearance was as follows: "There is connective tissue increase in the interstitial spaces, the vessels of which are surrounded by an inflammatory exudate. The latter is mainly composed of large mononuclear cells, with indented nuclei. Near the exudate, the muscle-fibres show advanced necrosis with phagocytosis. These changes can be found also in scattered muscle-fibres some of which show features suggestive of regeneration."

Discussion

When, by the end of July, 1960, the clinical picture had developed fully, this patient's condition conformed very closely to the classical descriptions of polymyositis. There was a story of subcutaneous œdema with transient arthalgia, and the subacute development of widespread weakness involving the facial, pharyngeal, and limb muscles. Muscle wasting was more pronounced around the limb-girdles than in the distal segments of the limbs. This distribution is highly characteristic, and has led in the past to confusion of this condition with muscular dystrophy, although the rate of progression of the muscular disorder in most cases of polymyositis suggested to some workers that they were dealing with a different disease. Its recognition as a nosological entity was delayed by the rigid views held about dermatomyositis. An acute or subacute muscular disorder without a coexistent rash was considered to be in a different category. The association of dermatomyositis with malignant disease was held to be very common, and the diagnosis was made reluctantly in the absence of evidence of neoplasia. Muscle biopsy and electromyography have led to the recognition of polymyositis in patients without neoplasms, skin lesions, or even muscle pain and tenderness: some patients have no constitutional symptoms either. These cases may be difficult to distinguish from muscular dystrophy (Walton and Adams 1958).

Siekert and Fleisher (1956) and Pearson (1957) reported raised levels of serum-glutamic-oxaloacetic-transaminase in patients with polymyositis. The level in our patient was not estimated until Oct. 4, 1960, when it was within normal limits (18 units per ml.). At this stage there was no clinical evidence of progression of the disease, and the estimation may have been made too late in its natural history. The level is likely to be high only while muscle necrosis is continuing.

Death in patients with polymyositis is not invariably due to this disease. In the group associated with neoplasms, death may be caused by the progression of the malignant disease. In the group of 40 patients reported by Walton and Adams (1958), there were 13 deaths during the period of observation: 7 of these were due to polymyositis and, of these, 5 were due to respiratory complications. These are a common cause of death (accounting for up to 50% of deaths in patients with severe dermatomyositis) and often they are associated with pharyngeal paralysis which leads to aspiration of oropharyngeal secretions into the lungs. Although polymyositis—particularly the acute and subacute varieties—is a disease of relapses and remissions (Garcin 1955), most patients who are alive a year after the onset are out of danger (Sheard 1951). Consequently, it is vital to attempt to tide the patient over relapses. The most dangerous single complication is pharyngeal paralysis, which may be followed by fatal aspiration pneumonia.

The patient who cannot swallow should not be nursed either sitting or supine: he must be semiprone or prone. If the dysphagia seems likely to persist for some time the airway should be protected by tracheostomy and insertion of a cuffed tracheostomy tube. It is then possible to assist respiration by intermittent positive pressure if spontaneous respiration fails.

We have been unable to find a report of the successful use of tracheostomy and I.P.P.R. in a patient with pharyngeal paralysis and respiratory failure due to polymyositis. This technique was obviously life-saving in our patient. The patient's disease is now in remission, but we do not know how long this will last. Remissions of nine (Weinberger 1933) and nineteen (Wedgwood et al. 1953) years have been reported. The disease can be regarded as controlled but not as cured.

Summary

Successful tracheostomy with intermittent positive-pressure artificial respiration in a patient with pharyngeal palsy and respiratory failure due to polymyositis is reported.

Respiratory failure was due to a combination of aspiration pneumonia and weakness of abdominal and intercostal muscles.

Protection of the airway by a cuffed tracheostomy tube, and adequate ventilation by a Radcliffe respirator, maintained life while antibiotics and physiotherapy combated the pneumonia and until the polymyositis remitted.

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THE ACTION OF CHORIONIC GONADOTROPHIN IN THE OBESE

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IN 1954 Simeons described the fat-mobilising powers of chorionic gonadotrophin derived from human pregnancy urine (C.G.). With daily injections of 125 units, patients were able to tolerate a 500-calorie diet for six weeks, during which time they lost an average of 20–30 lb. Simeons thought that C.G. led to the dispersal of fat away from the more favoured sites and that "fat in transit" might be more readily available for metabolic purposes than fat in "fixed deposit". He later elaborated this thesis (Simeons 1960); and Lebon (1961), using a similar technique, obtained equally successful results in obese patients.

RESULTS OF THE TWO TRIALS

Trial	Treatment	No. of patients				Average for patients completing trial							
		Starting trial		Completing trial		Age	Starting weight (lb.)	Weight loss (lb.) in week no.					Total weight loss (lb.)
		M	F	M	F			1	2	3	4	5	6	
I	Diet + C.G. injections	4	9	4	8	39	182	5·5	3·6	3·6	3·3	2·4	2·6	21·0 (14–31¾)*
	Diet + saline injections	4	8	4	6	40	185	5·2	3·3	2·9	2·6	2·8	2·2	19·0 (9–27¼)*
II	Diet + saline injections	2	9	1	7	34	183†	7·2	4·0	3·6	1·8	3·1	2·7	22·4 (14–27)*
	Diet alone	2	8	1	6	39	156†	5·6	2·6	3·3	1·0	2·4	2·4	17·7 (13½–20½)*

* Range of weight loss.
† Average starting weights were 178 lb. and 173 lb. for these groups respectively. Patients failing to complete the course were lighter than average in the first group and heavier than average in the group on diet alone, and this led to the larger difference in average starting weight for patients completing the trial. Analysis of the individual results showed that there was no relationship between starting weight and total weight loss.

In 1959 I began to use this treatment in my practice and obtained results comparable to Simeons'. Over 150 patients have since begun the course, in addition to the 46 referred to in this paper. Some, as always in these cases, defaulted from treatment, while others, though attending daily for their injection, did not keep to the rigid diet I had prescribed (based on Simeons' diet) and did not lose as much weight as those who did. Several patients returned for second, third, and even fourth courses of six weeks' treatment. Some came back because they did not lose enough the first time, others because they had too much fat to lose at one go and their loss, though adequate during each six-week course was not enough to bring them to a reasonable weight. Many have lost (in two or three courses) 4 and even 5 stones; 3 stones in two courses was not uncommon. Few of these patients have returned to their obese state. Others have returned for second and third courses because they had—over six months or a year—replaced all or most of the lost weight, and had found that the injections enabled them to lose weight where other methods had failed.

The Trials

From what my patients told me it was clear that rigid maintenance of the 500-calorie diet was essential if they were to lose anything like 20 lb. in six weeks. On the other hand, I wanted to know just what part the injections of chorionic gonadotrophin played in this treatment. Two trials were carried out.

In the first, two groups of patients were given either C.G. as described by Simeons or saline control. Both substances were presented to me in identical vials as a powder to be reconstituted (in the identical way Parke Davis present their chorionic gonadotrophin 'Antuitrin S'). The vials were numbered in random order. I did not know which contained C.G. and which NaCl until the trial was over. One vial of powder made up with 10 ml. solvent (the same solvent for drug and control) lasted one patient one full course of six weeks: they had 0·25 ml. daily for six days each week. In no case was a vial prepared for one patient and used for another.

In the second trial patients were selected from a random code either to undergo the diet plus the daily injections of saline or the diet alone. As each new patient presented, one of a series of numbered and sealed envelopes was opened. A card inside indicated to which group the case has been allotted.

I was thus able to compare the effects of C.G. on weight reduction with those of an inert control substance; and secondly, I assessed the value of a daily injection of the inert substance.

The results of both trials have been condensed into the table. In each week of the first trial, except the fifth, the average weight loss was slightly more in the group having the C.G. than in the group injected with saline. These differences were not significant at the 5% level.

In each week of the second trial the average weight loss was more in the group having injections of saline, but these differences were not significant at the 5% level. However the difference in average total weight loss in this trial was significant ($0{\cdot}01 < P < 0{\cdot}02$).

Discussion

The main point which emerges is that the stimulus of a daily injection helps the patient to lose weight. Why is this so? We must look at the facts a little more closely. In the second trial there was a further difference between the two groups. Those for injection not only had to come to my surgery six days every week, but they were also weighed by me on my scales every day. Failure to lose weight from one day to the next or even worse, the slightest gain in weight, led to a careful review by me of their previous day's diet. As one patient (a schoolmistress) said to me: "You know, Doctor, every time I look at a piece of food I think of what is going to happen when I get on your scales tomorrow morning." On the other hand, those on the diet alone had only to report to me twice a week to be weighed. We might presume that when they were tempted by food they may have said to themselves: "Never mind if I do eat it, I can always make up for it in the next couple of days."

It would be a boon to those who are overweight to have some drug that would enable them to lose weight safely without having to fight their appetite urges. C.G. is not an answer, nor does it seem appreciably to increase their weight loss if they do adhere to a very rigid 500-calorie diet. On the other hand, those on the diet alone constantly complained of feeling tired or weak. The patients on either C.G. or the inert placebo were keen to tell me how much benefit they got from the injections and how previously they had failed to keep to any diet they had tried (for obesity is usually a chronic disease and we rarely see a patient who has not tried other methods of shedding their excess weight).

One advantage of assessing such a therapy in general practice is that most of our patients come back to us, both successes and failures. We do not need to send for them for follow-up for sooner or later they return, even if it is only to have their passport signed before going on holiday or to accompany their children when they have their polio booster vaccination. This method, a 500-calorie diet supported by a daily injection, not only causes the patient to lose quite a bit of surplus fat rapidly (a psychological asset in any treatment is rapid success) but it also appears to help them re-educate their eating habits for

they rarely regain all their lost weight. Some continue to lose a little and then stabilise themselves; the majority, after losing 20 lb. or so, put back about 5 lb. and stay there for up to a year.

Over the two years I have used this method I have also noticed that the weight loss was most satisfactory in those who managed to attend my " group session ". Sitting in the waiting-room at 8.30 each morning they would compare notes. As each patient returned to the waiting-room from my surgery after being weighed and injected the others would eagerly ask for a progress report (or so my receptionist told me). New arrivals to the group would be encouraged by those already faring well. Fortunately those who fell by the way did not come back to heckle!

The treatment therefore seems to have some value and I now use injections of saline with good results. The weight loss from a 500-calorie diet maintained for six weeks is sufficiently high to act as its own testimonial for this treatment. Alas, it is difficult to persuade a patient to adhere to the diet without some stimulus. It would not be safe to restrict the diet for much longer than six weeks at a time because essential food items can easily be overlooked.

Summary

(1) Kept on a 500-calorie diet for six weeks, patients lose approximately 20 lb. in weight.

(2) In a double-blind trial, patients given daily injections of chorionic gonadotrophin lost slightly more weight than patients given a daily injection of saline. This difference was not significant at the 5% level.

(3) In a second trial patients weighed daily and given daily injections of saline lost significantly more weight than those weighed only twice a week and given no injections.

(4) Patients weighed daily under supervision seemed to find it easier to adhere to a strict diet.

I wish to thank Mr. G. T. Nelson, of Parke, Davis & Co., for supplies of ' Antuitrin S ' and control material.

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STAPHYLOCOCCAL SEPTICÆMIA

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IN the early stages of acute fulminating staphylococcal septicæmia, toxæmia may kill the patient before antibiotics become effective. Urgent measures are necessary and the administration of staphylococcal antitoxin may be lifesaving; the time gained gives antibiotics a chance to eliminate the infection. When, despite antibiotics, the response is inadequate, the administration of human γ-globulins may prove beneficial. The following case illustrates the value of combining these three therapeutic agents.

Case-report

A 16-year-old boy was admitted to the Western Infirmary, Glasgow, on Sept. 28, 1959. He had previously been fit, but two weeks before admission had received a mild injury to the left hip during a game of rugby.

On admission he was grossly dehydrated, breathless, and restless. There were tender erythematous patches on his forearms. He had widespread muscle stiffness, abdominal tenderness, and gross meteorism. His temperature was 102·4°F, pulse-rate 120 per minute, and respiratory rate 45 per minute.

Septicæmia was diagnosed, and a blood-culture was taken. Electrolyte and fluid disturbances were corrected. Pending the result of blood-culture, intramuscular penicillin 500,000 units 6-hourly was given. Despite this, the patient remained critically ill and was not expected to survive. He was restless and completely disorientated, with a continuous tachypnœa of 40–50 per minute. X-rays of the injured hip showed no abnormality. For a short time during the day after admission his blood-pressure became unrecordable and his pulse barely perceptible. Both forearms, the abdominal wall, and the left leg were œdematous. The limb muscles were very tender. Serum-enzyme estimations indicated severe tissue damage (aldolase 33·2 Bruns units, glutamic oxalacetic transaminase 150 Frankel units, and glutamic pyruvic transaminase 90 Frankel units). On the second day after admission the total-serum-globulin level was 1·05 g. per 100 ml. and electrophoresis revealed a distinct decrease in the concentration of the β and γ fractions.

On the morning after admission, the blood-culture showed a coagulase positive *Staphylococcus aureus*. Penicillin was continued for a further 24 hours. It was then reported that the organism was resistant to 0·5 units in the test medium and was a penicillinase producer. (Subsequently the organism proved untypable by the standard phages.) Penicillin was then replaced by chloramphenicol and erythromycin, to which the organism was sensitive in vitro. This, however, produced no clinical response, and three blood-cultures taken while the patient was on these antibiotics were positive.

On the 3rd and again on the 4th day 20,000 units of staphylococcal antitoxin was given. This produced a dramatic improvement but the improvement lasted only one day.

In view of the lack of response to chloramphenicol and erythromycin it was decided, on the 4th day, to recommence penicillin but at a much higher dosage of 36,000,000 units a day, in the hope that this might swamp the penicillinase production of the organism. (For the 1st week the penicillin was given by continuous intravenous drip, thereafter 6,000,000 units was injected 4-hourly intramuscularly.) Also on the 4th day, 1·5 g. of human γ-globulins was given intravenously followed by a further 1·0 g. on the 6th day.

Within 24 hours of starting the high dosage of penicillin and giving the first dose of γ-globulins a remarkable change took place. The patient's pulse, respiratory rate, and temperature fell to 110, 38, and 99·6°F respectively. He lost his mental confusion and for the first time looked as though he could survive.

The improvement continued; and, after 26 days, penicillin was withdrawn; the serum-γ-globulins became normal. In the 6th week after admission X-rays of the pelvis and hips showed clear evidence of septic necrosis of the left sacroiliac joint. Whether this arthritis was primary or secondary will remain in doubt; in either event the process must have been slow, possibly because of treatment. The patient was discharged from hospital after nine weeks when he was clinically well, although healing of the sacroiliac arthritis was not observed for a further 9 weeks.

Discussion

It is difficult to assess the contribution of each of the three therapeutic agents—i.e., staphylococcal antitoxin, γ-globulins, and antibiotics—used in the present case. The therapy was solely dictated by the patient's critical condition and the need for rapid improvement.

There can be no doubt that staphylococcal antitoxin had a beneficial effect in the early stage when the patient appeared to be moribund, and that this allowed time to be gained for subsequent measures. The effect, though short-lived, sufficed to tide the patient over. The results are in keeping with those of Blair (1958) and of Parish and Cannon (1960).

There is ample evidence of the value of giving globulins or combining them with antibiotics (Harris and Schick 1954, Knouf 1957, Fisher and Manning 1957a, Waisbren 1957), especially in a patient with low γ-globulins. Whether γ-globulins act by supplying natural antibodies or in a non-specific way is uncertain; but Fisher and

Manning (1957b) and Reedy et al. (1957) showed that removal of staphylococcus antibody from pooled human globulins deprived them of their effect in staphylococcal infections.

In the present case the infecting organism produced penicillinase; in-vitro growth was inhibited for 48 hours by approximately 3 units penicillin per ml. It was thought that large doses of penicillin might have a therapeutic effect; and it is likely, though by no means certain, that the final recovery of the patient was due largely to penicillin. At the time methicillin was not available.

Summary

A case of severe septicæmia caused by a penicillin-resistant *Staphylococcus aureus* is described.

Staphylococcal antitoxin produced shortlived improvement. Treatment with 36,000,000 units of penicillin daily was successful. The patient showed an initial γ-globulin deficiency, and on two occasions received human γ-globulins.

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A RARE ANTIBODY (ANTI-Ge) CAUSING HÆMOLYTIC DISEASE OF THE NEWBORN

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THE study of human red-cell antigens is intimately related to the isolation of the corresponding antibody. Such an antibody recently led to the discovery by Rosenfield et al. (1960) of the common "public" red-cell antigen designated Gerbich (Ge). These workers recorded three cases with anti-Ge. A further case is now presented, and we discuss the problems involved in the management of the patient and her pregnancy.

Case-history

A 21-year-old Turkish Cypriot primigravida presented herself on June 7, 1960, when she was 17 weeks pregnant. She had had no previous illness of note, no miscarriage, and no blood-transfusion. Clinical examination and a chest radiograph were normal. Her blood-group was O, Rh-positive. On routine screening of her serum with an R_1R_2rr cell mixture at 37°C, using an albumin-addition technique, antibodies were detected.

With the help of the Medical Research Council's Blood Group Reference Laboratory, and the South London Blood Transfusion Centre, further blood specimens were examined, with the following results:

The *husband:*

A_2 B; cde/cde; NS/Ns; Lu (a−); P_1+++; K−k+Kp (a−b+); Le (a−b−); Fy (a+ b+); Jk (a−b+).

The *patient:*

O; CDe/cde; Ms/Ns; Lu (a−b+); P_2; K−k+Kp (a−b+); Le (a−b+); Fy (a+b−); Jk (a+b−).

Furthermore, the patient's red cells were negative with anti-V, -Js^a, -Di^a, -Sw^a, -Wr^a, -By, -Mi^a, -Vw, V^t, and -Be^a. They were positive with anti -I, -Tj^a, and -Vel. The direct Coombs test was weakly positive, the coating being of the cold non-gamma-globulin type, and it was considered of little significance.

The antibody worked best as a cold agglutinin, and on testing it was found to agglutinate 160 random O-cell samples. It also reacted with cells of types Vel-negative, Tj (a−), Ko, and Lu (a+b−); but no reaction was detected with the 2 cell samples that were Ge-negative, and these cells enabled the presence of anti-E, -K, -Le^a, -Fy^b, -S, and -P_1 to be excluded. Titration of the antibody using random cell samples varied between 1/8 and 1/64 during the pregnancy, but no tendency for the titre to increase was noted in the later weeks of pregnancy after the antibody had been isolated.

Antenatal Care

Identification of the antibody as anti-Ge raised difficulties with regard to the antenatal care of the patient. We found that there were only three known Ge-negative subjects, all with antibodies; that over 10,000 blood samples had been examined in the New York City Rhesus Laboratory, 1000 samples at the Mount Sinai Hospital, and 500 samples at the Blood Grouping Laboratory in Aarhus, Denmark, without revealing a single Ge-negative blood-donor (Rosenfield et al. 1960). We were anxious to provide Ge-negative blood should either the patient or her baby require transfusion. There were three possible sources of a Ge-negative donor: first the immediate relatives of the patient, secondly the relatives of the three original cases, and finally the blood-donor panel in the United Kingdom. All had to be screened for a suitable Ge-negative donor.

Tracing the patient's relatives in Cyprus was difficult, but the search revealed an unmarried sister who, as well as being group O, Rh-negative, was Ge-negative without antibodies. Cross-matching later showed that her blood was compatible and could be given to the patient, if required.

In the 8 weeks before the birth the Blood Transfusion Service screened 16,000 donors without revealing a single Ge-negative subject; and a further 10,000 have now been screened, still without success. But examination of the relatives of the original cases showed that two of the three reported had either a brother or sister who was Ge-negative, thus bringing the total number of Ge-negative subjects to seven; and four of these carried anti-Ge as well.

During the 8 weeks before delivery the patient was bled several times; the plasma was used by the Blood Transfusion Service for their screening programme, and the red cells were returned to the patient immediately. 6 weeks before labour a pint of compatible Ge-negative blood was obtained from the sister in Cyprus in case labour should be premature. 2 weeks before the baby was due to be born, because no suitable donor had been detected, and the blood from Cyprus was nearing its expiry date, a pint of blood was taken from the patient. The cells (group O, Rh-positive, Ge-negative) were washed free of antibody, resuspended in fresh AB plasma, and stored in case either the mother or her baby should require a blood-transfusion.

Delivery and Postpartum Care

Because the antibody titre did not rise appreciably as pregnancy progressed, we decided not to induce labour prematurely. Labour began spontaneously at term on Nov. 24, and a healthy boy, weighing 7½ lb. was born normally after 26 hours. The total blood-loss was 5 oz.

The cord-blood bilirubin was 2·9 mg. per 100 ml. (indirect 2·1 mg., direct 0·8 mg.) and the hæmoglobin 11·8 g. per 100 ml. (75%). The direct Coombs test was negative. Nevertheless, the infant's pallor, slight jaundice, moderate enlargement of the liver and spleen, cord-blood anæmia, and hyperbilirubinæmia suggested that he had mild hæmolytic disease of the newborn. Because an exchange transfusion might be required, a further pint of blood was taken from the mother, and the cells were immediately washed free of antibody and resuspended in fresh AB plasma.

The serum-bilirubin 4 hours after birth was 4·0 mg. per 100 ml. (all indirect). 20 hours after birth the level had fallen to 2·9 mg. per 100 ml. (indirect 2·1 mg., direct 0·8 mg.) and the capillary Hb was 15·6 g. per 100 ml. (99%); this figure was thought to be influenced by the normal 1st day physiological hæmoconcentration. At this stage it was clearly obvious that

exchange transfusion would not be necessary. The serum-bilirubin levels continued to decrease, and 5 days after birth the infant was clinically normal apart from slight pallor. On further examination of the cord blood, the infant's blood-groups were found to be:

A_2; cde/cde; P_1++; Ms/Ns; Lu (a−b+); Le (a−b−); K−k+; Fy (a+b−); Jk (a+b+); Mi (a−); Vw−; Ge+; Vel+

and no free anti-Ge was detected.

The mother's recovery was uneventful, and the baby progressed satisfactorily, although 3 months later (when seen at outpatients), despite iron therapy by mouth, the Hb was 8·5 g. per 100 ml. (54%).

Discussion

There are now several well-established antibodies that react with the red cells of practically everyone tested. The case presented above is the fourth where such an antibody —anti-Ge—has been isolated.

The three other cases, reported by Rosenfield et al. (1960), resemble ours in several respects, although there are some differences:

A woman of Italian extraction (" Mrs. Ge ") presented in the same way as our patient except that antibodies were detected for the first time in her third pregnancy, her two previous children being normal. A normal infant was born, and although jaundice was not apparent the direct Coombs test was strongly positive.

A Mexican case presented when a third baby's cord blood gave a positive direct Coombs test. Investigation of the mother's serum then revealed an antibody which was anti-Ge.

In Denmark, a woman was found to have anti-Ge during her second pregnancy. The direct Coombs test on the cord blood was positive, and the baby became slightly jaundiced. A history of jaundice in her elder child during the 1st week of life unfortunately could not be followed serologically.

Our patient, like those of Rosenfield et al., presented during pregnancy, but unlike the others this was her first pregnancy. Although hæmolytic disease of the newborn was likely on clinical grounds (jaundice, pallor, hepatomegaly, splenomegaly), the direct Coombs test was negative. The Coombs test has been repeated several times, using different reagents, with consistently negative results; and this contrasts with the other three cases which were Coombs-positive although they showed less evidence of hæmolysis. But anæmia and hyperbilirubinæmia of the cord blood would suggest that the baby was affected apart from the clinical features; and, although preliminary investigations into the prevalence of Ge-negative subjects imply that this antibody is extremely rare, hæmolytic disease of the newborn (with or without a positive Coombs test) may be the result of an immune anti-Ge.

Including our case, four affected infants have so far been reported (three Coombs-positive). None of these has been so severely affected as to necessitate either premature induction of labour or exchange transfusion.

Summary

A case is described in which the anti-Ge antibody was detected during pregnancy. The subsequent management, involving the birth of a child with mild hæmolytic disease, required neither premature induction of labour nor exchange blood-transfusion.

We are indebted to Dr. T. E. Cleghorn, of the National Blood Transfusion Service, Sutton, for identification of the antibody and for the blood-grouping tests on the family; to Dr. F. Kissmeyer-Nielsen of Århus, who had two Ge-negative donors standing by; and to the medical authorities in Cyprus for their cooperation.

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Preliminary Communications

CLINICAL APPLICATIONS OF DEHYDROGENASE ISOENZYMES

A Simple Method for their Detection

By means of starch-gel electrophoresis it is possible, because of migration differences, to separate certain enzymes into a number of components—the so-called isoenzymes [1]—which are closely similar in their biological activity but have different pH maxima. Their distribution often differs from tissue to tissue, so that in certain conditions the isoenzyme distribution pattern of a diseased tissue may become manifest and recognisable in the serum,[2] presumably by leakage through altered cell membranes. These changes are especially evident after infarctions, and it is now well established that studies of serum isoenzymes of lactic-acid dehydrogenase are particularly useful after cardiac infarction.

The quantitative methods of detection are somewhat cumbersome and require many estimations for each patient; but we have developed a simple visualisation technique whereby serum-dehydrogenase isoenzymes can be studied very rapidly and in relatively large numbers of samples. The results obtained in relation to lactic-acid dehydrogenase are so promising in their clinical applications that the time seems ripe for a preliminary communication.

The technique employed depends upon the fact that lactic-acid dehydrogenase oxidises lactic acid, whilst at the same time it brings about the reduction of nicotinamide-adenine dinucleotide (NAD; formerly referred to as DPN) to its reduced form ($NADH_2$). The hydrogen of the latter is then utilised to reduce a tetrazolium salt to an insoluble coloured formazan. A substance must be used which is capable of carrying the hydrogen and handing it on for this final reduction. We have used methylphenazonium methosulphate; the tetrazolium salt we have employed is MTT (3-(4, 5-dimethyl-thiazolyl-2)-2, 5-diphenyl tetrazolium bromide) which is also used by others for a similar purpose.[3,4] The areas occupied by each isoenzyme after electrophoresis appear as purple bands.

METHODS

The isoenzymes were separated by vertical starch-gel electrophoresis by a technique [5] involving minor modifications of the method of Smithies.[6] The gels at pH 8·6 were made with 0·05 *M* tris-HCl buffer at pH 8·8 and hydrolysed starch obtained from the Connaught Laboratories (Canada). They were allowed to set for half an hour at room temperature and one and a half hours at 4°C. Each gel was 25 cm. long × 12 cm. wide × 0·6 cm. thick. A slot-former, as described by Smithies, was used to make insertions one-third of the way along the gel. One to ten slots were made, each of which was filled with 0·03–0·1 ml. of human serum or tissue extract, the quantity used being determined by the size of the slot. A voltage gradient of 10–12 volts per cm. was applied for two hours at 4°C with a bridge buffer consisting of 0·3 *M* tris-HCl at pH 8·6. After electrophoresis the gel was sliced with a fine wire along its whole length into sections approximately 1·5 mm. thick.

One of the inner slices was stained for lactic dehydrogenase by placing it in a solution containing 10 mg. NAD, 5 mg. KCN, 4 mg. MTT, 0·25 mg. methylphenazonium methosulphate dissolved in a mixture of 5 ml. *M* sodium lactate and 10 ml. of

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0·3 *M* tris-HCl buffer at pH 7·4 and then incubating at 37°C. The isoenzyme pattern showed up within two or three minutes, but thirty minutes in the incubator was allowed for full development.

Tissue extracts were prepared by homogenising a portion of tissue with approximately three times its volume of 0·9% NaCl in a Top Drive Macerator (Townson and Mercer), filtering through muslin, and clarifying the extracts in the ultracentrifuge at 100,000 *g* for thirty minutes. Each extract, prior to electrophoresis, was mixed with a small amount of normal serum which had been concentrated by ultrafiltration. The amount used was sufficient to restore the total protein content of the mixture to that of normal serum, and the mixture could be expected to give a similar isoenzyme pattern to that obtained in the serum of a patient with disease involving the particular tissue concerned.

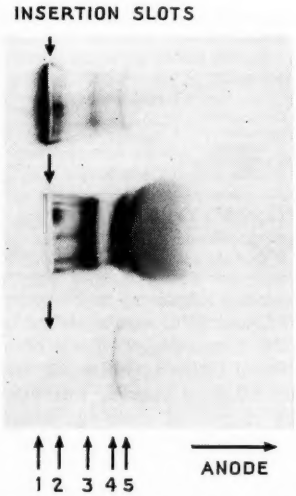

Fig. 1—Isoenzyme patterns obtained with a human liver extract (uppermost), a human heart extract (middle), and normal human serum. (The numbered vertical arrows indicate the positions of the various isoenzymes.)

RESULTS

It is known that lactic dehydrogenase occurs as five components—LD_1, LD_2, LD_3, LD_4, LD_5.[2 7] After starch-gel electrophoresis at pH 8·8, LD_1 appears on the cathode side of the insertion slot and the other components on the anode side, with LD_5 closest to the anode. The isoenzyme distributions we obtained after electrophoresis of a normal human serum, a human liver, and a human heart extract are shown in fig. 1. It will be seen that the serum components normally present are LD_2, LD_3, LD_4, and LD_5. LD_4 is the most prominent band, but it is relatively weak in intensity; and some of the other bands are so weak that sometimes they are not detectable. Obviously these bands must also be present in the tissue extracts, since they have been made up of normal serum, but the heart extract in addition shows a marked amount of LD_4 and LD_5 with some increase in LD_3, whereas the liver extract shows a well-marked band, LD_1, on the cathode side of the insertion slot, with possibly some increase in LD_2 and LD_3. The LD_5 band in the heart extract appears in the form of a well-defined narrow band and a more diffuse area arising from it and continuing towards the anode. This is due to the fact that some of the LD_5 becomes associated with serum albumin, and, as will be seen in fig. 2, LD_5 usually takes the diffuse form when present in the serum as a result of cardiac infarction.

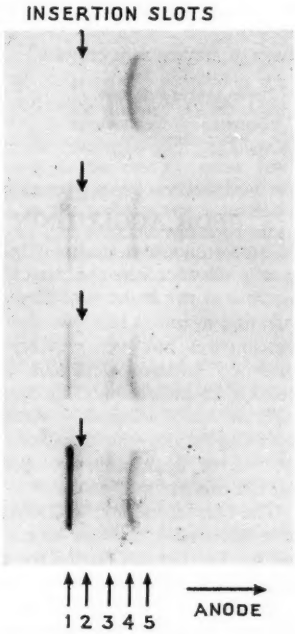

Fig. 3—Sera from three cases of hepatocellular jaundice compared with a normal serum (uppermost).

We have carried out serial determinations on the sera of five patients who had suffered a proven attack of cardiac infarction. Closely similar results were obtained in each case. A typical example is shown in fig. 2. It will be observed that the abnormal pattern closely resembling that of heart extract appears on the day after the infarction, soon reaches a maximum intensity, and then slowly fades. The pattern, however, is still detectable as abnormal on the fourteenth day after the initial attack. This is in spite of the fact that both the serum transaminase and lactic dehydrogenase had reached normal levels on the sixth day.

Some of the results we have been obtaining with sera of jaundiced patients are illustrated in fig. 3. Three such sera are shown and compared with a normal serum. It will be seen that only in the sera from the liver cases does an isoenzyme band, LD_1, appear on the cathode side of the insertion slot, whereas the bands on the anode side do not differ vastly from those of the normal serum.

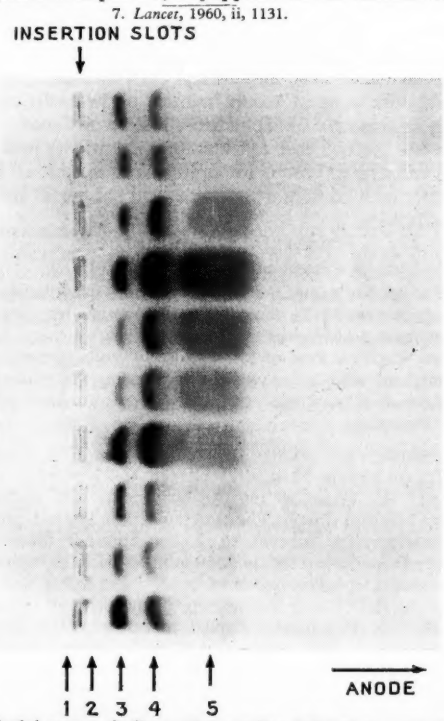

Fig. 2—Serial serum findings after cardiac infarction compared with normal serum (uppermost). The numbers on the left refer to the days after onset.

CONCLUSION

These observations seem to indicate that isoenzyme techniques of this type may well have important applications in clinical medicine. From our own and other [2] serial studies after cardiac infarction, it has become apparent that the isoenzyme pattern can remain abnormal even though other enzyme findings are within normal

7. *Lancet*, 1960, ii, 1131.

limits. This must be of great help to the cardiologist. Although this communication deals only with cardiac infarction and liver disease, there are undoubtedly a number of other conditions in which diagnostic help will be obtained. We are ourselves carrying out other studies in this respect. One interesting finding is the demonstration of isoenzymes in the cerebrospinal fluid after a cerebral catastrophe, whereas they are hardly detectable in normal fluid. We are also extending our studies to other dehydrogenase isoenzymes—e.g., those of malic and glucose-6-phosphate dehydrogenases—since the same technique is directly applicable. Moreover, by linking a dehydrogenation with another enzyme activity, the technique can be extended to the study of enzymes which do not belong to the dehydrogenase group. In this laboratory, it has already been used in this fashion in the study of serum transaminase.

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A NEW METHOD FOR AGGLUTININ ABSORPTION

EPIDEMIOLOGICAL studies of infectious diseases have been greatly advanced in the past 15 years by the enormous increase in the number of identifiable serological types of infecting agents. Identification of these numerous serological types, however, requires the use of a wide range of absorbed antisera; and the preparation of these has become an increasingly burdensome part of the work of medical bacteriologists. Accordingly it seems worth reporting briefly the development of a new and simple method of agglutinin absorption which would greatly lighten this essential work.

The current method of analysing the antigenic structure of a bacterial species or strain by agglutinin absorption has hardly changed during the 60 years that have elapsed since its introduction by Castellani.[1] It consists, essentially, of mixing a dense suspension of bacterial cells with a suitable dilution of antiserum (say at a concentration representing 64 times the known titre), incubating the mixture for several hours at 37°C, centrifuging out the cells, and testing the supernatant for unabsorbed antibody.[2]

One of the main uses of the method is the preparation of monospecific antisera for the identification of species or strains, as in the genus *Salmonella*. This may involve a series of successive absorptions with the same species or strain, or a succession of absorptions with different species or strains, each of which removes agglutinins corresponding to its antigenic structure. The method, though simple in principle, may be tedious in use and may result, in the course of successive absorptions, in the loss of much of the antibody which one wants to leave in the serum.

During an investigation of differences in the antigenic structure of flagella grown at 37°C and flagella grown at 20°C in a strain of *Escherichia coli*, the tedium and inefficiency of the classical method became painfully evident. (This search for antigenic differences had been prompted by the finding that flagella grown at high temperatures rapidly became paralysed whereas flagella produced at lower temperatures retained activity for long periods.[3] Antisera to H suspensions of cells grown at 37°C and 20°C were absorbed by cells grown at 20°C and 37°C respectively. Each antiserum before absorption showed a high agglutinating titre against homologous and heterologous flagella, but after successive absorptions the degree of cross-agglutination was much reduced. Antigenic differences between the flagella produced at different temperatures were thus revealed. Table I shows the results of an experiment of this kind.

TABLE I—AGGLUTINATION TITRES OF SERA PREPARED AGAINST H SUSPENSIONS OF CELLS OF *Esch. coli*, STRAIN WIG, GROWN AT 37°C AND 20°C BEFORE AND AFTER ABSORPTION WITH HETEROLOGOUS CELLS

Cells used in agglutination titration (H suspensions)	Agglutinating titres of antisera as reciprocal of highest dilution giving visible flocculation			
	Antiserum to 37°C cells		Antiserum to 20°C cells	
	Unabsorbed	Absorbed by 20°C cells	Unabsorbed	Absorbed by 37°C cells
Cells grown at 37°C.. ..	3200	320	800	Nil
Cells grown at 20°C.. ..	3200	40	6400	640

These results could be obtained only by a succession of absorptions extending over 1–2 weeks. Often the attempt to increase the specificity of the absorbed serum by one further absorption led to the disappearance of most of the specific antibody. This must be a common experience of those using agglutinin absorption in too perfectionist a way! In an attempt to simplify agglutinin absorption an adaptation of paper chromatography was tried; paper impregnated with heterologous cells was used as the stationary phase. The results suggested that removal of agglutinins could be achieved by this technique, but that it was, if anything, more tedious than the classical method. There was, however, the possibility that the principle might be capable of further application. A material, 'Sephadex', with interesting and novel properties had become available, and I decided to try to remove unwanted agglutinins by chromatography in which the column would consist of heterologous cells held in a matrix of sephadex. The results made it clear that the method had considerable potentiality as a simple and efficient technique for agglutinin absorption. Experiments with different antisera and bacteria show the possibilities.

MATERIALS AND METHODS

Cells Used for Absorption

The species or strain of bacterium to be used for absorption was grown for 18–24 hours, at the appropriate temperature, on meat extract agar slopes. Enough slopes, in 6 in. × $^5/_8$ in. tubes, to give a total of 100–170 × 10^9 cells (about six) were washed off with saline and the suspension was made up to a volume of 80–100 ml. with saline, or formolised saline for H suspensions.

Preparation of Absorption Column

Approximately 10 g. of sephadex G-25 powder, medium grade [4] was added to the cell suspension and stirred in to give a uniform slurry. The slurry was then poured into a glass chromatography column of 2 cm. internal diameter and allowed to sediment for about 10 minutes with the outlet closed. The outlet stopcock was then opened and saline was run off until no clear liquid was left above the column of sephadex. Thereupon the outlet cock was again closed. This gave a wet column of 15 cm. length and 2 cm. diameter consisting of sephadex plus bacterial cells. The volume of liquid to be displaced in each elution of the column was measured by adding a dilute suspension of indian ink to the top of the column, opening

1. Castellani, A. *Z. InfektKr. Hyg.* 1902, **40**, 1.
2. Cruickshank, R. *in* Mackie and McCartney's Handbook of Bacteriology; p. 327. Edinburgh, 1960.
3. Morrison, R. B. *J. Path. Bact.* 1961, **82**, 189.
4. Made by Pharmacia, Uppsala, Sweden. Obtainable in Britain from Samoore Ltd., Lawrence Road, London, N.15.

the stopcock, allowing the column to drain until all the indian ink had entered the sephadex, and measuring the amount of saline that had to be added to the top of the column to force the indian ink through to the effluent. This gave the V_0 value for the column, that is the volume of liquid held in the gel.

Agglutinin Absorption

10 ml. of a 1/10 dilution of serum, or a similar volume of undiluted serum, was added to the top of the column, which was allowed to drain until all the serum had entered the column. The outlet stopcock was then closed, and a vacuum flask fitted as effluent receiver. A volume V_0 of saline was added to the top of the column, the stopcock opened, and a negative pressure of 100-150 mm. applied to the receiver. When all but the last 13 ml. of saline had disappeared into the column, the stopcock was closed and the effluent collected up to that point discarded. The next 3 ml. and the following 10 ml. were then collected as separate fractions, and a further fraction of 5 ml. was obtained by the addition of another 5 ml. of saline to the top of the column. If the 10 ml. of diluted antiserum had travelled without spread, we should expect all the agglutinins to be present in the 10 ml. fraction, with the front 3 ml. and the back 5 ml. free of antibodies. In practice there was some, but surprisingly little, spread into the 3 and 5 ml. fractions. The 10 ml. effluent fraction was again added to the top of the column and the process repeated, the whole operation requiring 1–2 hours. When undiluted serum was used, a larger number of runs through the column had to be made in order to remove unwanted agglutinins. The effluent from the final run was tested for completeness of absorption by setting up agglutination titrations against homologous and heterologous cells.

Agglutination Titrations

The agglutinating titres of the sera were determined by the standard method described in a laboratory handbook of bacteriology.[2]

RESULTS

Antigenic Differences in the Flagella of Esch. coli, strain WIG, *Grown at 37°C and 20°C*

Two series of rabbits were immunised by a course of inoculations with H (formolised) suspension of cells grown at 37°C (first series) and 20°C (second series). When a sufficiently high agglutination titre had been reached, pools were made of the individual sera of the first and second series, and labelled 37° serum and 20° serum, respectively. The 37° serum showed an equal titre against flagella produced at 37°C. and flagella produced at 20°C. The 20° serum had a higher titre against the homologous 20°C cells than the heterologous 37°C cells. (table II).

Agglutinin absorption of the 37° serum was carried out by running either neat or diluted serum twice or three times through a column of sephadex containing 20°C cells, and of the 20° serum by running it through a column containing 37°C cells. Agglutination titrations were carried out on the unabsorbed and the absorbed sera against both types of cell. The results are shown in table II

That the agglutinations were due to flagellar antigen/antibody reactions was demonstrated by the findings that cells stripped of flagella by high-speed agitation [5] and 0 suspensions of the cells did not agglutinate with the absorbed antisera. That the absorption was not due to the action of sephadex was shown by the finding that a column of sephadex free of bacteria gave no differential absorption of agglutinins.

5. Stocker, B. A. D., Campbell, J. C. *J. gen. Microbiol.* 1959, **20**, 670.

TABLE II—AGGLUTINATION TITRES OF ANTISERA TO H SUSPENSIONS OF CELLS OF *Esch. coli*, STRAIN WIG, GROWN AT 37°C AND 20°C BEFORE AND AFTER ABSORPTION IN SEPHADEX CONTAINING HETEROLOGOUS CELLS

Cells used in agglutination titration (H suspensions)	Agglutinating titres of antisera as reciprocal of highest dilution giving visible flocculation			
	Antiserum to 37°C cells		Antiserum to 20°C cells	
	Unabsorbed	Absorbed by 20°C cells	Unabsorbed	Absorbed by 37°C cells
Cells grown at 37°C.. ..	3200	2560	800	<20
Cells grown at 20°C.. ..	3200	160	6400	2048

TABLE III—AGGLUTINATION TITRES OF *S. moscow* ANTISERUM BEFORE AND AFTER ABSORPTION IN A COLUMN OF SEPHADEX CONTAINING AN H SUSPENSION OF *S. enteritidis*

Cells used in agglutination titration (H suspensions)	Agglutinating titre of antisera as reciprocal of highest dilution giving visible flocculation*	
	Unabsorbed	Absorbed by *S. enteritidis*
S. moscow ..	2560	2000
S. enteritidis ..	2560	<20

* The absolute titres of the absorbed serum are 1/4 of the values shown.

Preparations of Antiserum Containing Agglutinins Specific to the Salmonella Antigen q

Antiserum prepared against H suspensions of *Salmonella moscow* containing the antigen gq was absorbed on a column containing an H suspension of *S. enteritidis* containing the antigens gm. The absorbed and unabsorbed sera were then titrated against H suspensions of *S. moscow* and *S. enteritidis*. The number of runs through the column needed to absorb out the unwanted agglutinin to g (in this case five runs) was determined by testing the effluent for slide agglutination of both organisms, and stopping at the point where a marked difference in the speed of agglutination with the two organisms was evident. In the experiment, the results of which are shown in table III, the serum was used at a dilution of 1/2 and underwent a further 1/2 dilution in the course of the five runs through the column.

DISCUSSION

The results of agglutinin absorption using as absorbing agent bacterial cells held in a matrix of the gel, sephadex, indicate that this technique has considerable advantages over the classical method. It is speedier and more efficient. To obtain similar results by the classical method of shaking cells with antiserum and centrifuging out the cells, six 24-hour absorptions had to be used to secure monospecific sera with the flagellar agglutinins of *Esch. coli*, strain WIG. This task occupied about a week and there was a great non-specific loss of the agglutinin it was desired to keep. By the column method five absorptions could be carried out in less than 5 hours; and there was a great diminution in the non-specific loss of the agglutinin it was desired to keep. That the method is not restricted to the particular organism for which it was first used is shown by the results of absorption of salmonella antiserum.

The essence of the method seems to be the successive exposure to the absorbing agent of the agglutinins to be absorbed, brought about in this case by distributing the absorbing cells throughout a matrix of sephadex. There is an analogy in the separation of closely related compounds by means of column chromatography where small differences in affinity between the compounds and the stationary phase of the column are magnified by successive exposure of the compounds to the absorbing force.

It is quite possible that other materials would act as supporting matrix to the bacterial cells, since there is no differential absorption when sephadex alone is used. Sephadex, however, can be mixed easily with the bacterial suspension, and the bacteria are not readily washed out of the column. With most of the alternatives that occur to one the bacteria would tend to be washed out of the column, or, if they were retained, the elution-rate would be tediously slow owing to the small pore-size of the column.

The method has obvious possibilities in agglutinin absorption both for antigenic analysis and in the

preparation of monospecific antisera. But it could probably be applied to other antigen/antibody systems provided conditions can be so arranged that the absorbing antigen is held in the column. For instance, it might be possible to remove specific viral antibodies by running antiserum through a column impregnated with virus particles.

SUMMARY

A technique of agglutinin absorption is described in which the absorbing agent consists of bacterial cells distributed throughout a column of 'Sephadex'. The results indicate that the method is speedier and more efficient than the classical technique of shaking cells with antiserum and subsequently removing the cells by centrifugation.

I am greatly indebted to Dr. J. S. Stevenson, of Stobhill Hospital, Glasgow, for supplies of salmonella antisera and cultures, and for much helpful discussion and advice. I am also indebted to Miss Joyce Hendrie for the excellence of her technical assistance.

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New Inventions

PORTABLE EQUIPMENT FOR GENERAL ANÆSTHESIA, GENERAL ANALGESIA, AND RESUSCITATION

MODERN anæsthetic equipment has reached a high level of efficiency, but unfortunately its weight and bulk make it almost immovable except over flat surfaces. Though this does not matter in hospital practice, there is a need for a really light and portable outfit enabling an anæsthetist to deal with the common problems of general anæsthesia, general analgesia, and resuscitation. "Portable" machines are available, but this is a relative term; in fact these models are really "transportable", and then only if the owner is in good physical condition.

For genuine portability, gas cylinders must be abandoned in favour of some type of "draw over" circuit using air. The Nuffield department of anæsthesia at Oxford has developed several such machines, and the latest E.M.O. portable unit, which uses ether and air, has a wide application; but its net weight is over 24 lb. It seemed possible to use a much lighter device for halothane, and an American apparatus has been described, under the title PUFFA (portable unit for fluothane anæsthesia).[1] In this a self-inflating bag, which is attached directly to a non-rebreathing valve and facepiece, draws its contents from a small vaporiser fixed to a retort stand.

In this country, after much trial and error, an apparatus of rather similar design has been produced from standard components. This seems to fulfil all essential requirements (the figure is self-explanatory). The assembly consists of:

A standard facepiece with harness attachment.

A Ruben non-rebreathing valve, which is standard except for a B.O.C. rubber bush to protect the pin of the outlet valve against inadvertent obstruction from towels, &c.

Corrugated tubing connected to a Goldman halothane vaporiser, which is mounted on a hollow wooden block to give stability.

A metal connection with a gas inlet normally sealed with a rubber cap.

An 'Ambu' self-inflating reservoir bag.

Accessory equipment.—Extra items will vary with the individual anæsthetist, but the following are suggested: a second smaller facepiece; assorted airways; an endotracheal adaptor and assorted cuffed tubes; laryngoscope; a 20 ml. and a 2 ml. syringe, carried sterile, with intravenous, mixing, and Mitchell needles; a tin containing ampoules of thiopentone, relaxants, atropine, neostigmine, pethidine, mephentermine, ergometrine, and aminophylline; an ether drop-bottle and mask; and ethyl chloride.

Portability and durability.—The whole of the above equipment will pack quite easily into one of the small overnight bags supplied by the airline companies. It is about a quarter of the weight and bulk of the E.M.O. unit designed for ether and air. The only part of the main apparatus likely to be damaged by rough use is the glass container of the vaporiser. This is well protected by being slung inside the wooden block; but, if it should be cracked, it can be replaced (as is well known) by an A.C. petrol-pump bowl, which is obtainable at most large garages.

Performance

When the apparatus is used for general anæsthesia, halothane is put into the vaporiser. After a thiopentone induction, the average premedicated patient will remain in a steady rather light plane of narcosis with the indicator set at 3. This corresponds to just under 2% vapour concentration, and unless the glass bowl is deliberately heated it is impossible to exceed about 2·2%. As with all types of draw-over apparatus, unless there is a gas-tight seal at the facepiece or at the cuff of the tracheal tube, dilution with air will lighten the plane of anæsthesia. The anæsthetist, using the apparatus for the first time, noting the immobility of the self-inflating bag, may think that the tidal respiratory volume is inadequate; but actually this is not so. For complete relaxation, gallamine (given through a Mitchell needle) is the most suitable agent; respiration can then be assisted or controlled by squeezing the bag. Ample vapour-flow for endopharyngeal insufflation (e.g., with a Boyle-Davis gag) is provided by moderate squeezing of the bag; if oxygen is available it can be added through the gas inlet. This inlet can also be used for nitrous oxide, and a straight "gas and air" can be given quite easily after a little practice.

If trichlorethylene is substituted for halothane, the apparatus can be used effectively for self-administered general analgesia in midwifery. With the drum position set at 2, 0·35% vapour is inhaled; and a setting of 3 corresponds to approximately 0·5% vapour. But, because the vaporiser does not conform to all the requirements of the Central Midwives Board, it should not be left in the charge of an unsupervised midwife.

For resuscitation the Ruben valve is connected directly to the bag, as in the original apparatus designed for treating respiratory paralysis.

With the equipment described above, the anæsthetist can deal with almost any contingency provided that some type of suction pump is available. There is always a temptation to try to improve simple types of apparatus, and in this case it might be thought that two flow-meters, or a more elaborate vaporiser fitted with temperature compensation, would add to the usefulness. But in my opinion this temptation should be resisted, because the apparatus is simply meant to provide adequate facilities with the greatest possible portability, and elaborations would destroy this primary object without making the apparatus comparable to the more highly specialised types available in hospital. Whatever may be the demerits of this equipment, it is unlikely to cause its owner an intervertebral disc prolapse.

I am indebted to Mr. L. Gibbons, of the British Oxygen Company, 27, Devonshire Street, London, W.1, for assembling the apparatus and for the illustration. This company can supply replicas if desired.

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1. Papanthony, M., Landmesser, C. M. *Anesthesiology*, 1960, **21**, 768.

Reviews of Books

Textbook of Clinical Medicine

Editor: JOHN W. TODD, M.D., M.R.C.P., physician, Farnham group of hospitals, Surrey. London: Pitman Medical Publishing Co. 1961. Pp. 564. 105*s*.

THIS new textbook gives a novel and valuable slant to the subject, and has the distinction of being edited by a physician of a non-teaching hospital. His nine colleagues cover a wide range of contemporary medicine from teaching and non-teaching hospitals in London and elsewhere.

Dr. Todd is renowned for his provocative criticism of much that is taken for granted in medicine, and the same spirit informs his book, compelling the reader to scrutinise carefully many traditional attitudes about the causes of disease and the treatment of patients. As the editor points out, not all diseases fall into the neat categories described in most textbooks; and he shows that much is still done in medicine on a basis of a-priori speculation or out of reverence for tradition. The past twenty years have seen a much more scientific and critical use of drugs, but this attitude has only just begun to extend to such things as nursing techniques, rest and activity, diet, and physiotherapy. His main concern, however, is to show the importance of emotional factors associated with bodily illness. Every physician learns this side of his job empirically as soon as he goes into practice or begins to see outpatients, but there is little guidance for him in most textbooks, and the attempt to fill this gap is Dr. Todd's principal service to his readers.

The most original chapters are those in which Dr. Todd sets out his philosophy of medicine. He grapples with difficult problems such as the handling of the neurotic patient with incurable symptoms, the treatment of the chronic invalid, and the care of the dying. He does not, however, say much about rehabilitation, surely one of the most important ideas in modern medicine.

The book describes the diseases of the body by systems in the conventional way; and each chapter contains a good section on clinical methods and diagnostic procedures. The sections on endocrinology by Dr. A. A. G. Lewis, gastroenterology by Dr. C. F. Hawkins, neurology by Dr. Michael Kremer, and respiratory diseases by Dr. F. H. Scadding deserve special mention. The illustrations are excellent.

This readable book succeeds to a remarkable extent in conveying the feel of contemporary medicine. It is perhaps more of a tract than a standard work of reference, but no-one who buys it is likely to feel regret. Its length is reasonable, perhaps because pædiatrics, mental illness, and skin diseases are omitted, but its price is notably greater than that of some of its well-established competitors. We congratulate the editor and his contributors on a major achievement.

The Chemotherapy of Tropical Diseases

Sir PHILIP MANSON-BAHR, M.D., F.R.C.P., consulting physician, Hospital for Tropical Diseases, London; JOHN H. WALTERS, M.D., F.R.C.P., physician, Hospital for Tropical Diseases, London. Springfield, Ill.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1961. Pp. 164. 56*s*.

THE authors of this monograph in the series of American Lectures in Living Chemistry accurately describe their work as an essay on chemotherapy with a reasoned synthesis of the epidemiological and ætiological peculiarities of the tropical diseases they have selected. The diseases appear under the headings: protozoal, spirochætal, rickettsial, bacterial, fungal, nutritional, climatic, metazoal, and venereal. The book ends with a useful list of drugs and their essential details.

The text makes easy and enjoyable reading, despite three different ways of presenting references. Common usage and the new *British Medical Dictionary* limit the word "chemotherapy" to the specific treatment by drugs of infectious diseases, but the authors' inclusion of nutritional and climatic disorders is welcome. There is no account of the treatment of leprosy or of blackwater fever. It might have been better to avoid the statement (table I, p. 9) that primaquine effects a radical cure of a clinical attack of malignant tertian malaria, since it implies inadvisedly that the drug might be used for this purpose; in fact the first choice lies with a relatively non-toxic schizonticide such as chloroquine. Two other points of less importance are that no mention is made of replacing potassium losses in cholera, and that the association of maize-eating with pellagra is discussed without saying that the cereal is deficient in tryptophan.

Some Aspects of Obliterative Vascular Disease of the Lower Limb

J. A. GILLESPIE, M.D., CH.M., F.R.C.S., senior lecturer in surgery, University of London, St. George's Hospital Medical School, London; D. M. DOUGLAS, CH.M., F.R.C.S., professor of surgery, University of St. Andrews. Edinburgh: E. & S. Livingstone. 1961. Pp. 136. 30*s*.

No reminder is needed of the uncertainties of peripheral arterial obliteration. The "insulin" discovery in atherosclerosis has yet to be made. In his introductory chapter on the pathology of arterial obliteration, Professor Douglas gives a clear and simple statement in the best Scottish tradition, although perhaps some might question the view that atheroma is ten times commoner in obese subjects than in lean ones, with intermediate grades according to fatness. The remainder of the book, by Mr. Gillespie, is concerned with a clinical and physiological study of patients with lower-limb occlusions. The hæmodynamic and sudomotor aspects of lumbar sympathectomy are well set out, being based on the author's well-known work on this subject. The case against vasodilators in peripheral vascular disease could not be better put. The place of operation in the more severe grades of ischæmia is not definitely vindicated, even though the lasting effects of sympathectomy on the physiological parameters are clearly established. A well-illustrated section on reconstructive arterial surgery, using good examples rather than of series of cases, illustrates the future trend in the treatment of this increasingly common disease.

Symposium on the Pathogenesis of Essential Hypertension

Editors: J. H. CORT, V. FENCL, Z. HEJT, J. JIRKA, Institute for Cardiovascular Research, Prague. Prague: State Medical Publishing House. London: Collet's. 1961. Pp. 469. 50*s*.

AT this symposium,[1] held in Prague in May, 1960, under the auspices of the World Health Organisation and the Czechoslovak Cardiological Society, the terms of reference were restricted, but the skilfully edited proceedings provide a volume of much interest.

Hood, from Sweden, described the changing picture of hypertensive disease during a decade of active treatment and emphasised the virtual disappearance of congestive failure as a cause of death, the sharp decline in uræmia, and the big increase in cerebrovascular accidents. Pickering reiterated his important thesis that high blood-pressure is inherited as a graded characteristic, that environmental factors are largely responsible for the rate of rise in pressure with age, that the difference between normal blood-pressure and hypertension is one of degree and not of kind, that essential hypertension represents the effects of a quantitative deviation from the norm, and that the ætiology is multifactorial. Particular interest lay in the contribution of five delegates from the U.S.S.R., who were active in all sections of the symposium. They seemed to be in agreement that hypertension is essentially a psycho-emotional disorder and based this on clinical observation in population and environmental groups and on animal experiments of the pavlovian type. As a logical consequence they laid great stress in treatment on rest, sedation, and environmental adjustments.

Brod from Czechoslovakia presented his data on regional blood-flows which demonstrate that the normal hæmodynamic response to emotional stress is similar to that evoked by muscular exercise, irrespective of whether the rise in pressure is due to an increase in cardiac output or to a rise in total

1. See Wilson, C., *Lancet*, 1960, ii, 1077.

peripheral vascular resistance. There is always a rise in vascular resistance in the kidney and skin (and probably in the splanchnic area) and a fall in the muscles.

Clifford Wilson concluded that although the kidney is probably concerned with the control of non-neurogenic basal arteriolar tone, there is no actual evidence that structural or functional changes in the kidney are concerned in the genesis of essential hypertension. He emphasised that the mechanisms responsible for chronic hypertension must be entirely different from those which operate in the early stages; and he thought it clear that hypertension could produce some change in a normal kidney which enabled it to sustain chronic hypertension, possibly through some extrarenal factor concerned with the distribution of body-water or electrolytes.

Peart held that there was little evidence to define any hormonal factor in any form of renal or essential hypertension and certainly none for circulating renin or angiotensin. He felt sure, however, that some circulating substance must be released by the kidney in response to interference with its blood-supply. Peterson, from the U.S.A., made an important contribution in describing his experiments directed to establishing methods by which the geometrical and mechanical properties of blood-vessels could be quantitatively evaluated. Clearly this was a fundamental step in clarifying the problem. Many factors might contribute to the control of blood-pressure, but the "final common path" must be some change in the response of the effector organ—the arteriolar wall.

A Brief History of the Hospital of Saint Bartholomew

GWENETH WHITTERIDGE, M.A., D.PHIL., F.S.A.; VERONICA STOKES, B.A. London: The Governors of St. Bartholomew's Hospital. 1961. Pp. 60. 5*s*.

ONE only of the medieval hospitals of London still stands upon its original site. A natural consequence of that distinction is that St. Bartholomew's has a history which is not only longer than that of any comparable institution but is also more complete. Visitors to Smithfield can still see a document which was sealed over 800 years ago by that same "jongleur" who fell gravely ill in Rome, and survived to create the foundation "for the restoration of poor men" wherein he is now buried. It is still possible to examine the list of duties with which Harvey was charged when he joined the hospital's staff, and to walk beneath the murals Hogarth painted when elected a governor.

It is the governors of the hospital who have commissioned the present short but profusely illustrated summary of its history. This is concerned with Barts, the institution, rather than with the many famous men who have worked there. But the reader will discover that Robert Bridges, the poet, was among them, and that Inigo Jones was baptised in its church. The hospital is unique in constituting a complete parish: and though the ownership of all other property within this parish is now vested in the Minister of Health, the church falls outside the provisions of the 1946 Act, and survives as a reminder of the traditional autocracy of a great teaching hospital.

C. G. Jung

E. A. BENNET, M.C., M.D., SC.D., D.P.M. London: Barrie & Rockcliff. 1961. Pp. 165. 21*s*.

Dr. Bennet has written an attractively informal account of Jung's childhood, early life, and subsequent development as a psychological investigator and philosopher. It does not aim at a complete biography but bears the personal flavour of the author's friendship with Jung over many years, during which he was often Jung's guest at his home in Küsnacht-Zürich.

Of most interest to the student of the history of modern psychology are the chapters on Jung's time at the famous Burghölzli hospital, under Bleuler, where he made his well-known researches into the word-association test invented by Dalton, and began his work on the psychogenesis of schizophrenia. This led to his association with Freud and with the early psychoanalytic movement in Vienna. Relations between the two great men were at first cordial, and Freud evidently saw Jung as his second-in-command, but underlying differences of opinion increasingly led to argument, culminating in a final and irrevocable rupture.

The rest of the book is concerned with exposition of some of Jung's theories, partly in the form of correspondence between him and the author; and the non-Jungian may regret that the great man is lost to sight in the mists of metaphysical speculation.

An Introduction to Clinical Electro-Encephalography

ROBERT R. HUGHES, M.D., M.R.C.P., physician-in-charge, neurological clinic, Royal Southern Hospital, Liverpool. Bristol: John Wright. 1961. Pp. 118. 30*s*.

ELECTROENCEPHALOGRAPHY is now widely used in the diagnosis of epilepsy and local brain lesions. We can, therefore, welcome an introduction to the subject suitable for senior clinical students and for physicians who make use of it but are not directly concerned with the procedure. This short book, after preliminary chapters on the normal E.E.G. and the technique used for recordings, describes the findings in epilepsy and in brain damage. The information is given under clinical headings. This is useful for reference purposes but tends to obscure the underlying changes in physiological activity which are the basis for E.E.G. changes. Chapters on psychiatric and biochemical conditions are included. Here also division into clinical groups obscures the logical presentation of the subject. The author recognises this point in his preface, but it becomes lost again in subsequent chapters. Nevertheless, as a short practical introduction the book will be useful for "those whose knowledge of the subject need only be limited".

The Friendly Societies in England, 1815-1875

P. H. J. H. GOSDEN. Manchester: University Press. 1961. Pp. 262. 32*s*. 6*d*.

As with most of our institutions and organisations, the roots of the National Health Service lie in the 19th century, and in the social problems and attitudes of that period; and the Service owes much to the experience of the friendly societies. This book is thought to be the first survey of the societies to be published since 1889. It shows how, in the earlier part of the 19th century, the societies were regarded as useful organisations for lowering the poor-rate, but dangerous in a political sense. But they were in fact pioneers of the self-help movement among the working men of the time. They were built up by working men to provide themselves with some security against the poverty and destitution resulting from sickness and death at a time when the State offered little. In 1815 the societies were small and local, with a total membership of less than 1 million. By 1875 the movement was dominated by great national societies, and had a total membership of 4 million. By developing contract practice the societies brought the services of doctors to many who could not have paid their own fees. At one time the movement overshadowed both the trade unions and the co-operatives until, towards the end of the century, political and social ideas had so changed that the friendly-society movement seemed to be a vested interest defending itself against change. The book is scholarly and readable, and contains much well-documented information.

Biological Activity of the Leucocyte (*Ciba Foundation Study Group no. 10*). London: J. & A. Churchill. 1961. Pp. 120. 12*s*. 6*d*.).—This book, edited by Dr. G. E. W. Wolstenholme and Miss Maeve O'Connor, records the papers given before a study group of 22 interested persons under the chairmanship of Prof. P. B. Medawar, and the subsequent discussions and arguments. The subject is very much in a state of development, and discussion rather than the formulation of definite conclusions seems to have been the object. It has often been said that we are relatively ignorant about the functions of white cells. This short book shows in which directions research is proceeding: on the functioning of leucocytes in tissue, on the importance of leucocytes in immune reactions, and on metabolic changes in leucocytes. Much of the material has already appeared in the journals, but it is useful to have so much of it collected together.

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London's Government

FOURTEEN months ago a Royal Commission unanimously recommended big changes in the government of London.[1] Feeling that the pattern of authority has become too confusing, and that the London County Council, in particular, has acquired too much power compared with the Metropolitan borough councils, the Royal Commission was concerned to make town halls once more the focal point of local administration. To this end it proposed that the primary administrative unit should in future be the " Greater London borough ", of which there would be some 52, each with a population of 100,000–250,000. These boroughs would be fully responsible for, among other things, the whole range of services relating to personal health, welfare and children's care, and they would undertake the day-to-day management of schools, including the school health service. To look after the needs of London as a whole, there would be a Council for Greater London, covering an area much larger than that of the L.C.C. This new council would be the education and planning authority, and the authority for traffic, main roads, refuse disposal, and the fire and ambulance services.

Against these proposals the L.C.C. and other bodies brought some telling arguments.[2] First, can we be sure that the uncertain advantages justify the very certain upheaval? The suggested reforms involve the disappearance of the counties of London and Middlesex, the truncation of Essex, Kent, and Surrey, reduction in the size of Hertfordshire, reduction in the status of three county boroughs, and reorganisation of some 70 authorities of the second tier. " Almost every service which had hitherto been organised as a whole by one authority would be dismembered, divided, and distributed ", and the period of transition would be very difficult. While agreeing that municipal services ought not to be impersonal, the L.C.C. pointed out that much depends on the local-government officer, and it doubted whether some of the smaller authorities would be able to recruit an adequate staff. Moreover the new boroughs would not really represent local communities but " have been suggested according to an artificial and arbitrary criterion of size ". Supporting these criticisms, the Local Medical Committee for London did not like the idea of handing the personal services back to Metropolitan boroughs with widely differing methods and standards:

" The commission have planned for the Londoner a collection of boroughs where everyone can take part in local politics; but, though this may have been appropriate for a Greek city State in 500 B.C., it is not therefore suitable for a 20th-century London. What the Londoner really wants is good administrative government, and by and large, so far as County Hall is concerned, he is satisfied that he has got it."

The London Executive Council similarly expressed its preference for a system in which the same arrangements and procedures apply over the whole area. " If the local health services were fragmented over a number of boroughs it would immensely complicate the work of the family doctor."

Cogent though these objections are, we cannot for our part regret that the Government have decided to embark on the course marked out by the Royal Commission. The commission rightly said that the L.C.C. has provided a " strong and able form of government which makes its standing very high among the municipal governments of the world "; and, if immediate efficiency were the only criterion, few would want to do more than modify the present system. But there is a great deal to be said for the principle by which a proportion of the tasks of government are left to the people of the locality; and the L.C.C., in providing for so large a population, has ceased to offer local government in the sense in which this was formerly understood. There is a chance that, if the boroughs are skilfully constituted, restoration of important functions to them will lead to a renewal of democratic life in their communities. Judging by the apathy of the public towards all forms of government, the auguries are not entirely favourable; but the attempt seems worth making, even at considerable cost. Contrary to the intentions of its proponents, universal suffrage has made people feel impotent in national politics: what effect can one vote have among so many? But in local elections, if the issues were such that they really mattered to a community, a man's vote might once more come to seem valuable to him. Moreover, if the boroughs had real responsibilities for the local and personal services, they would attract into local government more men and women of real ability.

In endorsing the Royal Commission's main conclusion that the boroughs ought to become the primary unit of local government, and that a new authority should be elected for purposes concerning Greater London as a whole, the Government make two important modifications.[3] One of them is that the boroughs should be larger, and therefore fewer, than the commission proposed; the other is that education should be not only administered but also planned, by the boroughs (though in the heart of London there would probably have to be a large education authority for an area comprising several boroughs with a population of perhaps 2 million). The Government, aiming at a unit which would be efficient in action and strong in resources, suggest that the " London boroughs " (as they are to be called) should wherever possible have a population of *at least* 200,000. In the white-paper they agree with the commission that, except for the

1. Royal Commission on Local Government in Greater London. Cmnd. 1164. H.M. Stationery Office. 1960. See *Lancet*, 1960, ii, 963.
2. See *Lancet*, 1961, i, 549.
3. London Government: Government Proposals for Reorganisation. Cmnd. 1562. H.M. Stationery Office. 1961. Pp. 12. 1*s*.

ambulance service, all personal health and welfare services, and children's services, should become borough responsibilities; and they concur in the belief that positive advantages will come of concentrating responsibility for these services, and other associated ones, such as housing and environmental health, in the hands of the same authorities. Reserve housing powers, however, should be conferred on the Greater London Council, which should be solely responsible for arrangements for overspill outside the area. This council "should be empowered to build within the area if and only if that is necessary to help a borough unable to solve its own problems, or to secure development in accordance with the development plan". We note with pleasure that the Government agree with the Royal Commission that the Greater London Council should set up "a first-class intelligence department for continuous research into the many interlinked problems of Greater London as a whole, a department which should serve not only the authority itself but also the borough councils, the central Government and the public".

As the white-paper says, the legislation required to give effect to these proposals will be extremely complex, and many subjects will need to be explored with the local authorities before a Bill can be brought before Parliament. The present aim, however, is that the new authorities should be elected in the autumn of 1964 and they should take over in the following April. The Government want to avoid delay, because, they say, the changes proposed will provide, for this city of more than 8 million people, "a more effective and a more firmly based system of local government, better fitted to meet the needs of the future".

New Penicillins

Now that the nucleus of penicillin, 6-aminopenicillanic acid,[1] has been isolated, penicillins with new side-chains can be prepared fairly readily, and Beecham Research Laboratories alone have synthesised many hundreds. Two at least of these have made possible the treatment of infections previously regarded as resistant to penicillin. It is not surprising, therefore, that a steady stream of new penicillins are appearing on the market and that other firms are entering their production. This is to be welcomed, since penicillins, apart from hypersensitivity reactions, are the least toxic of antibiotics and, because of their bactericidal action in high dilution, among the most effective. Even the fact that several are similar in action is of no great significance, provided the similarities are kept in mind.

Up to a few weeks ago, four new penicillins had appeared—each, alas, under several different names. They are, in order of appearance: α-phenoxyethyl penicillin (phenethicillin, 'Broxil'); 2:6 dimethoxyphenyl penicillin (methicillin, 'Celbenin', 'Staphcillin'); D(−) α-aminophenyl penicillin (ampicillin, 'Penbritin'); α-phenoxypropyl penicillin ('Brocillin', 'Ultrapen'). The second and third of these, methicillin and ampicillin, represent an important advance.

Methicillin, as is now well known, is almost completely resistant to staphylococcal penicillinase, and is therefore invaluable in the treatment of penicillin-resistant staphylococcal infection. Against penicillin-sensitive bacteria, however, it is much less active than benzyl penicillin; and since it is not resistant to acid, it has to be given by injection. Also it is expensive. For these reasons, as well as because of the possible danger of breeding new types of penicillin-resistant staphylococci, methicillin should be reserved for the treatment of severe penicillin-resistant staphylococcal infection, in which it is the drug of choice.

Ampicillin[2–4] has a broader spectrum than the other penicillins on the market. Compared with benzyl penicillin, it is considerably more active against gram-negative bacilli and *Streptococcus fæcalis* though equally (or only slightly less) active against other gram-positive cocci. Most strains of salmonella and shigella appear to be sensitive to it in concentrations of 1·25 μg. per ml. or less,[2 4] and many strains of proteus and *Escherichia coli* are sensitive to 2–5 μg. per ml. Strains of *Hæmophilus influenzae* and *parainfluenzae* are usually sensitive to benzyl penicillin in concentrations of 1 μg. per ml. or less, and these are about twice as sensitive to ampicillin. Being resistant to acid, ampicillin can be given by mouth[3] and a preliminary report indicates that it is effective against urinary infections due to *Esch. coli* and/or group-D streptococci.[4] It has been found disappointing in the treatment of salmonella carriers. It is readily inactivated by penicillinase from staphylococci and other bacteria, and partly for this reason most strains of *Klebsiella aerogenes* and some strains of *Esch. coli* and proteus are resistant to it.

The other two compounds, α-phenoxyethyl and α-phenoxypropyl penicillin, are closely related to penicillin V, which is α-phenoxymethyl penicillin. All three are acid-resistant and can therefore be given by mouth. In tests in vitro, with most penicillin-sensitive bacteria the order of activity is phenoxymethyl, phenoxyethyl, phenoxypropyl; but as regards absorbability after oral administration the order is reversed. Since the difference of in-vitro activity of the three compounds is less evident with streptococci than with other bacteria, it has been suggested that phenoxypropyl penicillin would be more effective than the other two in the treatment of streptococcal infections, and that, therefore, this compound is likely to prove the most generally useful oral penicillin.[3] A point which has so far been overlooked, however, is that plasma-binding is considerable with α-phenoxypropyl penicillin but only slight with phenoxyethyl and negligible with phenoxymethyl penicillin. Further comparisons of the three compounds in clinical practice may reveal other differences. Meanwhile the fact that phenoxymethyl penicillin is much the cheapest of the three cannot be ignored.

1. Batchelor, F. R., Doyle, F. P., Nayler, J. H. C., Rolinson, G. N. *Nature, Lond.* 1959, **183**, 257.

2. Rolinson, G. N., Stevens, S. *Brit. med. J.* July 22, 1961, p. 191.
3. Brown, D. M., Acred, P. *ibid.* p. 197.
4. Stewart, G. T., Coles, H. M. T., Nixon, H. H., Holt, R. J. *ibid.* p. 200.

Last month the Distillers Company announced the introduction of yet another compound (phenoxybenzyl penicillin, 'Penspek'), which was claimed as "the most effective oral penicillin for general use"; and in the near future Bristol Laboratories Inc. hope to put on the market a penicillin which is said to be resistant both to staphylococcal penicillinase and to gastric acid, and can thus be given by mouth. It is also reputed to be more active than methicillin against penicillin-sensitive bacteria.

Thus the story, happily, is still "to be continued".

Growth of the Eye

THE bodily proportions change considerably during growth. The skull and face hardly grow at the same rate as the axial skeleton, and the different systems—and perhaps even tissues—all appear to have growth-rates of their own. The growth of the central nervous system is complete long before skeletal growth ceases, whereas the reproductive system grows little until the onset of puberty—by which time skeletal growth is nearly complete in girls, but not in boys.

The fact that in most myopes the shortsightedness develops about puberty has suggested that refractive errors may be related to growth. Data on the growth of the eye are remarkably sparse, and consist largely in findings established on the cornea in life and on the axial length post mortem. As early as 1890 PRIESTLEY SMITH [1] drew attention to the rather surprising fact that the corneal diameters—readily measured in life—had reached adult size by the age of 5 years. Subsequent investigators have put the age even lower, and the corneal dimensions may possibly have reached adult values by the age of 2 years. That the rest of the globe follows a different pattern of growth was suggested by the work of WEISS. In 1897, WEISS [2] reported postmortem measurements of the dimensions of the globe at different ages in childhood, and these rather pointed to growth being complete by the age of 8 years. As for the individual components of the eye—the curvatures of the cornea and of the lens, and the thickness of the lens—very little is known beyond the fact that the lens is more spherical in infancy than in adult life. Failure to obtain such data has been due to lack of adequate techniques for measuring the components of the eye during life, and to the difficulties in obtaining material for detailed postmortem studies.

SORSBY, BENJAMIN, and SHERIDAN [3] have now described observations which go far towards establishing the pattern of growth of the eye in children from the age of 3 years. Using a photographic method for recording images of a light source on the cornea and on the anterior and posterior surfaces of the lens, and measuring the depth of the anterior chamber and the thickness of the lens by a slit-lamp technique, they obtained the necessary data for computing the axial length by the method of conjugate foci. With apparatus designed by them, measurements were carried out quickly and accurately in children as young as 3. With the help of the London County Council they made these measurements in a cross-sectional study of about a hundred children in each age-group from 3 to 15 years. In addition they followed up some 400 children for periods ranging from two to six years. From the results a remarkably simple pattern emerges. In the first place the cross-sectional study shows growth to be completed by the age of 14 years; and the increase in axial length between the ages of 3 and 14 is of the order of 0·1 mm. a year, regularly distributed throughout this period. The total growth of the eye therefore amounts to little more than 1 mm. from the age of 3. Any lengthening of the eye is a potential cause of myopia, and lengthening of the order of 1 mm. would reduce the refraction of the eye by about 3 dioptres. Actually the amount of reduction observed was about half, since there was an associated flattening of the lens and to some extent also of the cornea. Secondly, the follow-up study showed that the averages obtained in the cross-sectional study could not be applied uncritically to an individual child. The average lengthening of the eye by 0·1 mm. per year was lacking in some children, and was represented in others by considerably more—up to 0·7 mm. in a few cases. Abnormal axial lengthening would readily precipitate myopia; but myopia was found only exceptionally, for, where axial elongation was pronounced, flattening of the lens and cornea was also pronounced: hence refraction was very much the same in eyes that grew but slightly and in eyes that grew notably. Ocular growth by itself—and even considerable growth—does not therefore produce a refractive error, but brings about a compensatory process. Fine automatic adjustment takes place in the eye during growth from the age of 3.

These findings bear out an earlier study by SORSBY and his associates [4] on the nature of refractive errors. They showed that the emmetropic eye has a wide range of values for each of its optical components—the cornea, the anterior chamber, the lens, and axial length—and that in the emmetropic eye the different components are adequately correlated, whilst in eyes with up to 4 dioptres of myopia or hypermetropia the self-same range of components are found but are inadequately correlated—i.e., they have the wrong corneæ and lenses for their particular axial lengths. SORSBY et al. emphasised that most refractive errors were to be regarded, not as the result of the free association of components of refraction nor as the result of anomalous components (i.e., components not met in emmetropia), but as a derangement in correlation. Myopia and hypermetropia in excess of 4 dioptres are present in some 6% of the population,[5] and in this small section an anomalous component is generally responsible for the refractive error.

These studies establish that refractive errors are due not so much to anatomical defects as to failure in the physiological mechanism of adjustment—a failure which

1. Smith, P. *Trans. Ophthal. Soc. U.K.* 1890, **10**, 68.
2. Weiss, L. *Arb. anat. Inst., Wiesbaden*, 1897, **8**, 191.
3. Refraction and its Components during the Growth of the Eye from the Age of Three. By ARNOLD SORSBY, B. BENJAMIN, and MICHAEL SHERIDAN, with the assistance of JANET STONE and G. A. LEARY. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1961, no. 301. H.M. Stationery Office. Pp. 67. 9s. 6d.
4. Sorsby, A., Benjamin, B., Davey, J. B., Sheridan, M., Tanner, J. M. Emmetropia and its Aberrations. *Spec. Rep. Ser. med. Res. Coun., Lond.* 1957, no. 293. See *Lancet*, 1957, i, 827.
5. Sorsby, A., Sheridan, M., Leary, G. A., Benjamin, B. *Brit. med. J.* 1960, i, 1394.

SORSBY et al. postulated for the adult eye and have now demonstrated in the growing eye. The view that anomalous components—particularly an anomalous axial length—determine refractive errors has been almost unquestioned dogma for well over a century. Clearly this dogma—valid enough for the small group of cases of high myopia and high hypermetropia—is not justified as a comprehensive explanation of refractive errors; and likewise the view that refractive errors result from the free association of normally varying components [6] is apparently untenable.

The photographic techniques applied so successfully by SORSBY et al. to the study of growth in older children were found unsuitable for infants under the age of 3 years; but certainly between birth and this age the changes are much more extensive than those that occur later. The axial length of the globe in the full-term child at birth is just short of 18 mm.,[7] compared with about 23 mm. at the age of 3; and this growth gives a potential 20 dioptres of myopia unless drastic flattening of the cornea and lens occurs at the same time. Clearly therefore there is a rapid infantile phase of growth concentrated in the first 3 years of life, and this is followed by a relatively slow juvenile phase from the age of 3. The nature of the changes in the first 3 years and their influence on the ultimate refraction of the eye have yet to be determined.

6. Steiger, A. Die Entstehung der sphärischen Refraktionen des menschlichen Auges. Berlin, 1913.

7. Sorsby, A., Sheridan, M. *J. Anat., Lond.* 1960, **94**, 193.

Annotations

TRAINING FOR FAMILY PRACTICE

IN planning its symposium of Nov. 26, the College of General Practitioners gave equal time to training of the doctor and training of the student. At first the former was felt to be the larger problem; and there were many conflicting ideas about its solution. Should the vocational training of graduates be mainly "in service" or by an undirected drifting from diploma to diploma in hospital, and should there be university departments of general practice offering postgraduate courses? On the training of the student there was more initial agreement, but it was really only agreement about the magnitude of the difficulties—difficulties both more subtle and more fundamental than those of training the graduate. When it comes to the point, what is the object of our undergraduate education? At what stage in the curriculum should vocational matters (such as the techniques of general practice) intrude? How much should changes in the medical needs of the community itself affect what the student is taught? And, behind it all, where is family medicine going, anyway? Is it to be a subject for specialists or generalists? A first-line of medical care, or an anachronism?

All these uncertainties are accentuated by the speed of change in medicine, which shows us repeatedly that we should no longer be trying to cram everything into the undergraduate years. Somehow we must stop this "ribbon development" of medical education and choose what to keep and what to throw out. The problems are made more urgent by the long wrangles in the curriculum committees, over which the advice of the General Medical Council—to instruct less and educate more—hangs like a continuing (and now quite long-established) challenge.

To many speakers the main function of undergraduate training was to produce a doctor who has learnt to think scientifically. To them the content of his training does not matter much, so long as it serves this end. Future roles, and particularly the possibility of his becoming a family doctor, are thus largely irrelevant; for vocational training can be started after graduation. Opposed to this view are those who devise attachment schemes and are concerned that the student should learn about the vocation of family medicine from the men on the job. To them the need is for more and earlier teaching about the work of the general practitioner, and they would press for more dermatology, more therapeutics, or more psychiatry, because these subjects are so much needed by the family doctor in his day-to-day work. Between these extremes of view are to be found two groups of medical teachers, and their supporters among the family doctors. Each is concerned with the underrepresentation in the medical curriculum of a newly important aspect of medicine.

The first group, who owe much of their inspiration to Dr. Michael Balint and what the Americans call "the-patient-is-a-person" school, are increasingly preoccupied with emotional relationships in medicine. Because to them the doctor's job is now primarily psychotherapeutic, they feel that this change in attitude should be reflected in undergraduate teaching. Increasingly this teaching should be aimed at the development of psychiatric insights and skills and be focused on the family.

A second group, inclining to the view that the function of the curriculum is to induce a scientific outlook, believe that family medicine should concentrate on prevention. Looking a long way ahead, they see the family doctor spending much of his time determining who is particularly vulnerable among his patients and then offering medical care to them even before they feel ill. This change in family medicine is regarded as one inevitable result of the rapid increase in the proportion of all illness which is due to chronic and degenerative disease, much of which is already incurable when symptoms appear. It is argued that the change of attitude and skill likely to be needed to practise this sort of medicine is so great that even a highly scientific undergraduate training would have to adapt considerably to meet it. Since the diagnosis of who is vulnerable in a population must turn so much upon the bringing together of epidemiological knowledge and knowledge about family habits and ways of living, it is hard to see who could practise preventive medicine (or treatment before there are symptoms, which was thought to be the same thing) except the family doctor. For these reasons, this group hope to see, throughout the undergraduate curriculum, an increasing bias towards family and preventive medicine.

Fortunately, very few of the ideas discussed at this symposium are wholly incompatible. Perhaps a few departments of family medicine, headed by full-time professors, could undertake some of the vigorous experiments—in preparing both students and young doctors for family medicine—which have become so clearly necessary. Present trends in disease suggest that the quality of medical care in family practice will soon be of critical importance.

RADIOBIOLOGICAL RESEARCH

THOUGH it has been called " the medical section of Harwell ", the Radiobiological Research Unit of the Medical Research Council is constitutionally quite independent of the great empire of the nearby Atomic Energy Research Establishment. The unit was founded in 1947 to investigate the fundamental action of ionising radiations on living systems; and it lay at first within the security fence of the A.E.R.E. In 1953 the work was transferred to the present building outside the forbidden area. These more spacious quarters made it possible to move to Harwell the work on mammalian genetics promoted by the M.R.C. at the Institute of Animal Genetics in Edinburgh. Though the unit is now on the other side of the fence, its staff still have the obvious advantages of close contact with those working on matters of pure nuclear energy and the use of Harwell's unique devices and their products. Last week the unit, which is directed by Dr. J. F. Loutit, held an " open day " to demonstrate some of its research; and the work on display ranged from topically relevant studies of fission-product metabolism to less spectacular and more protracted inquiries into the induction of mutations in mice exposed to repeated low doses of radiation.

The results of Dr. A. G. Searle's mouse experiments are, so far as they have gone, odd. 18 variants in the mouse skeleton were studied in successive generations of irradiated mice of an inbred identical strain, and the results were compared with the findings in control lines of unirradiated animals. The exposed mice received 1r per night for up to three years; and evidence was sought of " subline deviation " in the skeletal characters that would suggest mutation. Unexpectedly, the variation in the control mice was greater than that in the irradiated group. What this means remains to be seen, but at this stage the experiment certainly cannot be interpreted as in any way disturbing the accepted relation between radiation and mutation. What it does demonstrate is the complexity of this kind of analysis and the difficulty of uncovering with certainty what low doses of irradiation can do. Large experiments prolonged for many years may supply an answer—and still leave the question of how far it applies in man. In experiments which Dr. R. H. Mole, deputy director of the unit, called " the first sighting shots at trying to find out what happens when mutations are released into a population ", Dr. J. Godfrey is studying a mixed population of mice in which the offspring of irradiated parents can be identified by means of a marker gene (producing a black-and-tan mutation) and their ability to survive and reproduce can be assessed. The animals were kept in population cages designed so that the mice could choose their own mates and yet be accessible to regular and complete enumeration and examination. Descendants of 600r-irradiated mice were distinctly fewer than those of the control strains.

The metabolism of both short-lived and long-lived fission products is being investigated. Short-lived products of bomb tests are collected from the air and fed to rabbits. The uptake and distribution of isotopes of iodine, strontium, barium, tellurium, and molybdenum are then determined. The absorption and retention of long-lived radiostrontium is of special interest. Its transfer across the intestine has been measured in vitro, and assessed in animals on diets differing in calcium and strontium content. And Dr. G. E. Harrison, Mr. T. E. F. Carr, and Dr. Loutit put themselves on a diet containing small amounts of radiostrontium. One objective was to decide whether the human body treated strontium from grain in the same way as strontium from milk. A cow that had been given strontium 85 supplied the milk, so that milk-strontium could be distinguished from grain-strontium, which was the 90 isotope. No difference was detected in the body's handling of the two sources. In this country milk is the chief dietary source of strontium: in many parts of the world most of the intake is from grain.

INFECTIVE HEPATITIS

IT is humiliating to realise that, despite technical advances, there are still diseases of presumed viral origin in which the causal organisms have not been isolated and characterised. Prominent among these have been infective hepatitis and serum jaundice.

That the cause of infective hepatitis is viral was suggested by Findlay et al.[1] in 1939. This hypothesis was much strengthened by a series of studies in which volunteers were infected with material derived from patients. This work established (*a*) that infectivity resides in the serum during the preicteric stage, (*b*) that the infective agent is moderately heat-resistant and passes bacteria-tight filters, and (*c*) that infective hepatitis and serum jaundice each has a distinct and characteristic incubation period.[2] Attempts to isolate a causal virus in the laboratory have involved trials in many animal species from the miniature pig to the canary, fertile eggs, and several kinds of tissue-culture systems. Though some results of these painstaking efforts seemed promising at first, they have remained largely unconfirmed.[3]

In 1956 Rightsel et al.[4] reported the isolation from patients with infective hepatitis and serum jaundice of a group of transmissible agents cytopathic for cultures of certain cells of human origin. Because of the previous disappointing results, this report was received with some reserve. Earlier this year Davis [5] reported the isolation of 13 viruses from the stools of children with infective hepatitis. These viruses gave characteristic lesions in a line of tissue-culture cells of human origin and did not grow in other animal cells. They were all serologically related and were distinct from known viruses; further they were neutralised by convalescent hepatitis serum. There was no direct evidence that they caused hepatitis.

Now Rightsel et al.[6] and Boggs et al.[7] report from the U.S.A. further virological studies and clinical trials with viruses isolated from cases of infective hepatitis. The results are striking. There seems no question but that these workers have isolated a group of viruses comprising at least three serotypes. When these viruses were inoculated parenterally, they caused disease clinically indistinguishable from infective hepatitis even after several passages in tissue culture. The viruses, which proved amenable to conventional virological techniques, have to some extent been characterised. The particles seen in electron micrographs are among the smallest recorded—12–18 mμ. in diameter, a size commensurate

1. Findlay, G. M., MacCallum, F. O., Murgatroyd, F. *Trans. R. Soc. trop Med. Hyg.* 1939, **32**, 575.
2. See Havens, W. P., Jr., Paul, J. R. Infectious Hepatitis and Serum Hepatitis in Viral and Rickettsial Infections of Man; p. 269. Philadelphia, 1948.
3. See Symposium on the Laboratory Propagation and Detection of the Agent of Hepatitis. Publication 322, National Academy of Science, National Research Council, Washington D.C., 1954.
4. Rightsel, W. A., Keltsch, R. A., Tekushan, F. M., McLean, I. W. *Science*, 1956, **124**, 226.
5. Davis, E. V. *ibid.* 1961, **133**, 2059.
6. Rightsel, W. A., Keltsch, R. A., Taylor, A. R., Boggs, J. D., McLean, I. W. *J. Amer. med. Ass.* 1961, **177**, 671.
7. Boggs, J. D. Capps, R. B., Weiss, C. F., McLean I. W. *ibid.* p. 678.

with filtration and ultracentrifugation data. Infectivity was retained after heating (in serum) to 60°C for 30 minutes and was resistant to ether.

This work represents a great stride in the elucidation of human hepatitis, but much remains to be done. For example, we need to know how many serological types of virus are involved and their relative virulence. Only then may we learn enough about the natural history of such infections to make some rational approach to prevention. The American workers are to be congratulated on plucking a ripe but elusive plum. It remains to be seen what kind of pie can be made with it.

LUNG LININGS

THE lining layer of the lung has always held the greatest interest for physiologists, clinicians, and pathologists. The lung-lining film, which is the frontier between air and tissue, is the subject of two papers from the Chemical Defence Experimental Establishment at Porton.[1 2] Pattle has been investigating this lining film for some years and has shown that its outstanding characteristic is a very low surface-tension—of the order of 0·05 dynes per cm., compared with 30–50 dynes per cm. for most biological fluids. He has demonstrated this low surface-tension by squeezing air from small pieces of lung into a drop of water hanging on a microscope slide, and then measuring the size of the bubbles. In air-saturated water ordinary bubbles, a fraction of a millimetre in diameter, disappear in a few minutes under the influence of their own surface-tension. Bubbles from lung do not vanish in this fashion; instead, they usually decrease in size a little and then remain stable. The ratio of their final surface-area to the initial value is called the " stability ratio ". Bubbles from lung which behave like this are called " normal bubbles " and their stability ratio is around 0·7, whereas the stability ratio of ordinary bubbles is zero. There is a correlation between the behaviour of lung specimens and the stability ratio; the lower the stability ratio, the more readily does the lung fall back to an almost air-free state. Prattle suggests that a normal lining film, indicated by normal bubbles, is necessary if the alveoli are to remain open.

The capacity of the lung to form this lining film, as measured by the stability ratio, seems to be unaffected by bronchial obstruction, blast, indirect injury, or early inflammation, or by irritants, provided these are not surface-active. After intratracheal instillation of surface-active substances such as lecithin, lysolecithin, and Tween 80 the formation of a lining film is defective: this may be because the foreign substance covers the lining complex. Lecithin and lysolecithin are potential decomposition products of lung-lining complex itself.

Pattle has also investigated the lining film in the fœtus. Hyaline-membrane disease in children, or the corresponding " barker " syndrome in thoroughbred foals, is associated with the signs to be expected from failure of a lining film to form. The first conclusion from the fœtal work is that spontaneous aeration of the lungs takes place only when the capacity to form a complete lining film appears. The second conclusion is that this capacity appears when the cuboidal-epithelium lining is lost; and in man, since this occurs at about 24 weeks of gestation, it seems unlikely that hyaline membrane disease, or the more general pulmonary syndrome of the newborn, is due to the lung's inability to form the film. A possible cause of the disease is contamination by a surface-active substance inhaled in amniotic fluid, so that although the lining film has appeared it is masked. Pattle suggests that the correlation of the disease with cæsarean section may be explained in this way, since the lungs of infants so delivered will contain more amniotic fluid at the time of the first breath than will the lungs of a normally delivered child.

1. Pattle, R. E., Burgess, F. *J. Path. Bact.* 1961, **82**, 315.
2. Pattle, R. E. *ibid.* p. 333.

OPPORTUNITIES FOR RESEARCH

FROM the days of Osler, and indeed long before, it has been recognised that the transplantation of doctors can be a valuable stimulus to their own work and thought and to the practice of their new country. The medical profession of this country has an honourable record of service overseas, but for some years there has been a regretful feeling that some of our younger doctors are emigrating for negative rather than positive reasons. They seek opportunity elsewhere only because it is lacking at home. Uneasiness is felt especially about the possibilities for research. Emigration of too many of the fittest will hinder medical progress here, and some years ago we pointed out [1] that already medical faculties often found difficulty in filling professorial chairs.

Since resources are limited, it is important that they should be used effectively and that support should be given to the right people in the right form. Several " distributing bodies " have lately made sensible adjustments and experiments. The Royal College of Physicians of London, for instance, has offered research fellowships which will allow a consultant to combine research and clinical practice.[2] The Scottish Hospitals Endowments Trust has altered its policy so as to give scope to experienced investigators and opportunities for training in research to promising juniors.[3] The latest prophylactic scheme has been put forward by the Wellcome Trustees who propose in 1962 to offer one or two senior research fellowships. Professors in charge of university departments of medicine, surgery and obstetrics are being asked to nominate outstanding candidates. The purpose of the awards is " to ensure that workers of high promise as clinical investigators are not deprived of opportunity by lack of an academic vacancy at the appropriate time ". It will be a condition of the appointment (which will carry a stipend of £1900 × £150—£2500 over five years) that the fellow should be granted the status and responsibilities of a lecturer in the university department in which he works and should have practical control of a number of patients under the nominal supervision of the professor. If possible, he should be given consultant status, but routine clinical and teaching duties should not take more than six hours of his time each week. The Trustees hope to make a limited number of similar awards in subsequent years.

ARCHITECTURAL SERIES

Dr. Beddard's article on the next page of this issue concludes the series which, under the title From Words to Wards, has appeared week by week since Oct. 28. A booklet containing the seven articles in this series may be had (3*s.* 3*d.* a copy, post-free) from *The Lancet*, 7, Adam Street, London, W.C.2.

1. *Lancet*, 1958, ii, 677.
2. *ibid.* 1960, i, 661.
3. *ibid.* Nov. 18, 1961, p. 1154.

From Words to Wards

7. CONCLUSION

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IN professional circles today the capacity to write may tend to outstrip the inclination to read; but anyone who has stayed the course thus far and is willing to complete this last lap will, it is hoped, reflect on his reactions during the earlier circuits of the track.

The main purpose of the series is to bring the doctor into closer communion with the architect by tracing the part each has to play in the planning of hospitals, and to identify the points of contact between the two professions. After nearly twelve years of the National Health Service it may well be asked why a method of planning has not been developed and polished smooth. In fact during these early years administrators and medical staff alike have been so occupied with putting their house in order and patching part-worn buildings that, in some measure, we are ill prepared to plan on the grander scale.

The desire of the hospital services and of the public —the real clients—to build, and build quickly, calls for new planning methods. It is vital that the doctor and the architect work with understanding and find a means of communication which does not waste each other's time. Each must have the capacity to know when the other has not grasped his point and the charm to be able to say so without offence. They must enjoy each other's company without being too intimate, lest they grow casual and uncritical. The architect with an artistic environment and upbringing may find it difficult to appreciate the scientific mind: the doctor may appear to treat æsthetics with the disregard of the Philistine. In truth, however, beauty and function are complementary as is witnessed by the ugly strivings of the landlocked swift compared with its glorious beauty in effortless flight. Sommerville and Wightman [1] developed this theme and gave it practical expression in the first article of this series, and Cowan [2] ably analysed the problem of communication in the second.

The Four Acts

Planning can be divided into four main stages which must be differentiated if doctors and architects are not to dissipate their efforts, for the role of each differs in the four stages. These four are: (1) planning for need; (2) functional planning, or the preparation of the brief for the architect; (3) designing; and (4) equipping and commissioning.

Planning for Need

Planning for need is the process by which it is determined whether a new hospital or extension to a hospital is necessary and possible, and, if so, what its broad content should be in terms of the service which it will provide and the policy which it will pursue. The initiative for this stage normally falls to the board of governors or the regional hospital board and its advisers. The board, if it is wise, forms a joint planning committee with the hospital management committee or board of management, with Ministry of Health or Department of Health officials present, so that decisions on matters of broad principle can be taken in concert. When agreement has been reached and clearly recorded, the architect, engineer, and quantity surveyor should be appointed; and general questions of the quality of the proposed site and its suitability for development are discussed. The main elements of the project are identified and thought is given to the way these elements can be grouped.

Functional Planning

The second stage is functional planning and the preparation of the brief for the architect. Too often in the past he has had to do this himself; but it is the task of the client, not of the architect. This task is best undertaken by a small group of staff responsible to the joint planning committee; the size of the group, varying from one to a maximum of eight, depends on the size of the project. For the small project, the one—perhaps a medical administrator—should be free to consult individually or together whomever he thinks can contribute. For the larger project, the group should contain representatives of the main disciplines involved. They must be prepared to study their subject; and they should be free to give much time to their task, the leader of the group, at least, being whole-time on this work for as long as this stage of planning lasts. To Leslie's [3] qualities of ability, integrity, foresight, and good humour, I would add youth as an essential for the planning team. They should not necessarily be the heads of the departments concerned, who may be wiser to reserve their experience for constructive criticism at a later stage. The task of the group is to commit to paper the functions they hope will be carried on, why they will be carried on, how they will be carried on, and who will carry them out. (It should be noted that no mention yet is made of where they will be carried out.) In compiling this document, after the group as a whole has settled certain principles, each member may be given a section which he writes after consulting members of staff and others, individually or in concert, bringing his work back to the main functional planning group. This group should get to know the architect and refer to him if necessary; but it is often claimed (and previous contributors to this series have suggested) that the architect should be a member. In my view he may waste much time in listening to sterile argument, and indeed his presence almost invariably leads to obsession with space rather than function. The temptation for the amateur architect of the group to draw squares on paper becomes irresistible, and some members may be overawed by "the expert". It is said that the architect will find his scope restricted unless he has taken a prominent part in the preparation of the functional brief; but if the brief is confined to a description of functions and procedures, and if its authors are ready later to revise their conceptions in the light of architectural considerations, then I do not believe that an architect can fail to rise to the challenge of finding solutions to the functional problems. The chapters of the ideal functional brief are headed, not "operating suite" but "operative surgery", not "medical ward" but "medical in-patient care", not "kitchen area" but "catering services". Florence Nightingale knew the meaning of functional planning. She wrote to Galton, the Inspector General of Fortifications, in 1861:

"Your draft does not define with sufficient precision the manner in which the meat is to get from the Commissariat into the soldier's kettle and the clothing from the Quartermaster's Store on to the soldier's back."

Where there is doubt whether old procedures seem

1. Sommerville, T., Wightman, A. *Lancet*, Oct. 28, 1961, p. 974.
2. Cowan, P. *ibid.* Nov. 4, 1961, p. 1027.
3. Leslie, I. M. *ibid.* Nov. 11, 1961, p. 1080.

sensible, it may be necessary to experiment with other methods, submitting them to work study or other forms of measurement. Many data are now available from overseas and, more recently, from guide material prepared by the Ministry and Department of Health.

The last chapter—and I emphasise the word last—of the functional brief is the schedule of accommodation or list of rooms, and this fails easily into place provided the functions have been clearly described and firm decisions taken. In my view, this schedule should not include instructions as to the actual size of each room, for the manipulation of space is one of the architect's main skills. Tatton Brown,[4] quoting Philip Johnson as saying " Architecture is thrown away space ", has drawn attention to the enormous possibilities in the use of proportion and scale. He has pointed out, for instance, that the eye subconsciously adopts as a yardstick familiar things such as a moulding or skirting; and, by using detail of minimum size with everything else in proportion, rooms can be made to appear larger and give a feeling of freedom. The miniature garden exploited so skilfully by the Japanese is an example of this technique.

For this stage of planning, I see no alternative to the written word as the means of communication; and, however much the architect prefers visual techniques, the doctor is entitled to expect a capacity to read, provided he protects the architect from jargon, ambiguity, and circumlocution.

Design

The third stage of planning is design. Here the architect comes into his own. He is the designer and takes over the initiative and his position as leader of the team. The functional planners must be at his side to make sure he understands how they intend to work, and they must learn his pictorial language so that they can judge whether his design will permit the functions to be carried out. At the early stage of designing the doctor need not feel shy to crave alternative schematic drawings and rough sketches. In my experience, architects are only too pleased to repeat their work at this stage, if only, as Cusdin [5] emphasised, to avoid expensive and time-consuming alterations later when much detail has been already prepared and variation means chaos. The functional planners must be prepared to compromise with architectural and æsthetic considerations and to cooperate with the designer in any experiments to test the validity of functional ideas. Much lip service is paid today to the need for adaptability and flexibility; but if the architect is to use his skill and cunning to achieve this end, he must not be hampered by the inflexible demand of the doctor to have designs tailor-made to his individual requirements on the basis of his preconceived notions. If the functional brief has been well conceived and clearly set down on paper, as Oddie [6] has suggested, the architect's chances of reaching understanding and achieving inspiration will be greatly enhanced. He can thus be given a chance to understand the few, through whom the ideas of the many have been channelled.

Equipping and Commissioning

The fourth stage is equipping and commissioning. Many of the decisions concerning fixed equipment will have been taken during the functional and design planning stages; but the architect, or his mate—the interior decorator—must be given free rein to advise on the design, colour, and texture of equipment so that the whole will be in harmony. Many of us like to think that we have impeccable taste, a high sense of colour value, and an eye for design. In fact, most are hopelessly ignorant, colour-blind, prejudiced, and inexperienced in these matters. When a matron chooses the curtains, the secretary selects the furniture from a pre-war catalogue, the clerk of works picks the linoleum from a limited range, the chaplain decides on the pictures which are to be hung on the wall, and the whole is rounded off by a vase presented by the worthy chairwoman of the board of management whose husband happens to run the souvenir stall on the pier, then the hospital is in for serious trouble. If the architect knows and understands the functions which the hospital is to perform, his skill will permit him to exploit colour, space, and the abundant choice of finishing materials to the greatest advantage.

I have already emphasised the need for understanding between doctor and architect in their performance of this four-act play; but their efforts will miscarry unless they respect the position of the rest of the company. The central departments, as trustees for the citizen patron, have a duty to procure value for money however elusive this prospect may seem. The planners should realise this if they wish to avoid a curb on the progress of their work. It is not difficult for architect, engineer, and doctor to urge each other on in a frenzy of endeavour to a standard of provision which, while not extravagant on its own, nevertheless attracts to itself an undue share of the total resources. " O! when degree is shak'd, which is the ladder to all high designs, the enterprise is sick." In Scotland—to which my experience has been limited in recent years—it is pleasant to record that the rein is but lightly applied where evidence of reasonable restraint is shown. Contrary to ill-informed opinion, the central departments and boards are just as anxious to achieve good hospitals as those who will work in them. But, whereas the individual planner is naturally less enthusiastic about other projects which may be competing for finance, he is more likely to achieve his aim if he is in sympathy with those who have to take a less parochial view and to see the individual job against the background of the building programme as a whole. Happily the consultant or professor who reports with triumph that he asked for twice what he needed expecting to be cut by half but has got away with it all has almost disappeared. Such a philosophy is utterly inconsistent with good planning. While the need for streamlined methods involves, as has been shown, small professional committees with wide powers of decision, the part that the boards themselves can and should play is too easily forgotten. At the end of the day they carry the responsibility and bring a healthy and practical influence on the projects they promote. While many members of boards will wish to leave consideration of detail to officers in whom they have confidence, architects and doctors alike do well to remember that they work on behalf of these appointed representatives of the citizens whom they in their turn serve.

Research

A word on the need for research. Allen [7] in his article sadly reflects that in hospital design, though there is much innovation on a small scale, the " deeply penetrating developments " often escape us. He attributes this rightly to the large number of clients and thus the lack of ideas with clear identity and general support. Medicine is a highly personal combination of science and art, and its high priests are as individualistic as they are dogmatic.

4. Tatton Brown, W. *Listener*, Aug. 31, 1961, p. 309.
5. Cusdin, S. E. T. *Lancet*, Nov. 25, 1961, p. 1189.
6. Oddie, J. A. *ibid.* Nov. 18, 1961, p. 1135.
7. Allen, W. A. *ibid.* Dec. 2, 1961, p. 1244.

How else can they promote faith in and obedience to their counsel? The development of the medical team is comparatively recent. Furthermore, the introduction of the National Health Service was a social upheaval of the greatest magnitude from which the dusts of disturbed prejudices are only now beginning to settle. The hospital is no longer a vehicle for the dispensation of charity but, instead, the abode of the owner when sick. The basic attitudes to hospital care are changing, and all must agree with Allen that the need for operational research in the light of these new attitudes should proceed. Of the many doctors, architects, administrators, and others at present engaged in actual planning for the current building programme, should not more be spared for fundamental research into the hospital needs not of this decade but those that are to follow?

* * *

For those who have run their laps and breasted the tape, this series of articles will have emphasised the heavy responsibility of the doctor, whether practising clinician or medical administrator, in his role as planning agent for the public. I hope it will also have drawn attention to the tremendous opportunity before the medical profession of this generation and the immense satisfaction to be won by furnishing our great National Health Service with the buildings it deserves.

Conference

ARTERIAL DISEASES

THE new Nuffield Institute of Comparative Medicine is the only centre in this country which aims at combining veterinary and human medicine into a single science. At the first conference of this institute, held, under the chairmanship of Sir ROY CAMERON, at the Zoological Society of London on Nov. 22, vascular disease in man and animals was discussed.

The main objectives of the meeting were to discover the existing research interests in comparative cardiovascular disease and the contribution which might be made by the new institute in furthering such studies, and to consider the correlation of research under the auspices of the World Health Organisation.

Sir SOLLY ZUCKERMAN welcomed the speakers and visitors, and launched the new institute.

The role of the World Health Organisation in cardiovascular research was described by Dr. M. M. KAPLAN, head of the public-health section of W.H.O. He emphasised the value of seeing the human problem in a new perspective, by means of comparative animal studies. W.H.O. could play a valuable part in coordinating work from various research centres on naturally occurring arterial disease. He outlined some projects which might be useful. The first was a study of atherosclerosis in swine. This omnivorous animal had many features in common with man, and the arterial lesions in the pig's aorta somewhat resembled human atherosclerosis. It was important to discover the frequency of these lesions in pigs from different countries which had different methods of animal husbandry. Such studies, he thought, might cast some light on ætiological factors. Secondly, Dr. Kaplan was concerned with the need for more intensive study of arterial disease in poultry, where again some knowledge of the part played by dietary factors might emerge. Thirdly, studies of closed colonies of animals, such as that in California on the beagle hound, were important. Sir HAROLD HIMSWORTH emphasised the need for a starting hypothesis in biological research. This could often be gained by a view of Nature's own experiments illustrated by the comparative study of cardiovascular disorder.

Dr. D. K. DETWEILER, director of the Cardiovascular Studies Unit at Philadelphia, outlined the research going on in the U.S.A. on cardiovascular disease. In comparing human and animal atherosclerosis the following questions needed to be answered: to what extent were the lesions in man and animals similar; had any animal counterpart of the human lesion been found; were the mechanisms involved in the production of lesions the same? Any differences between human and animal lesions might not be fundamental, but might rather be due to differences in modes of life. Since vascular disease was probably the end-result of many factors, studies of lesions must be supplemented by functional and structural studies of vessels.

Prof. THEODORE CRAWFORD gave a detailed account of the various stages of the human atherosclerotic lesion. This provided a baseline for subsequent discussion of arterial lesions in other species. He suggested that incorporation of fibrin into the arterial wall was possibly a pathogenetic factor in atherosclerosis, and he provided histological and experimental observations to support this view. He recalled recent histochemical studies of ^{35}S uptake and of enzymes in atherosclerotic lesions, and said that more might be learned from histochemistry now that fresh operation specimens of arteries were becoming more readily available. He then sounded a note of caution on the translation of results of in-vitro studies of blood coagulation to the conditions prevailing in an artery and indicated recent work on fibrinolysis which was relevant to the problem. The half-life of fibrinogen labelled with ^{131}I seemed to be of the order of five days. This suggested a considerable turnover of fibrinogen to fibrin and removal by fibrinolysis. Factors such as postprandial lipæmia which influenced fibrinolysis might, therefore, play some part in atherogenesis.

Dr. J. E. FRENCH illustrated atherosclerotic lesions found in the aorta and large vessels of old pigs from four years of age and more. The distribution of the lesions was similar to that in man, and the histological characteristics had some similar features He indicated, by elegant electron micrographs, that smooth-muscle cells were present and probably played an important role in the development of these lesions. Sir ROY CAMERON commented on the need to review the structure of normal vessels in a variety of species.

Prof. W. I. B. BEVERIDGE summarised the various studies on comparative cardiovascular disease which were being conducted in the United Kingdom: in Glasgow, work on atherosclerosis in birds and the effect of œstrogens, in Edinburgh on canine coronary-artery disease, at the London Zoo on arterial disease in captive animals, in Cambridge on arterial lesions in wild birds and pigs, at Babraham on the reactions of arteries in disease, and at Newmarket on horses and dogs.

Dr. R. FINLAYSON and Dr. C. SYMONS described and illustrated a range of arterial lesions found in animals examined post mortem at the London Zoo. Lesions were commonest in birds, and fatty streaking appeared to be replaced by raised plaques as animals became older. 50% of vultures and eagles had lesions, whereas the penguin had few if any. Thrombosis was rarely associated with the arterial lesions which they had observed in animals.

Sir HOWARD FLOREY emphasised the need for a study of arterial disease in animals without too rigid adherence to human criteria. A detailed study of groups composed of a few selected examples would probably achieve more than a cursory study of a large number of creatures. He welcomed the formation of the new institute as a place where widely scattered information on comparative medicine could be correlated. This could best be done by occasional meetings of interested individuals. He indicated the importance of studying hæmodynamic problems in an animal comparable in size to man and the need for detailed study of selected species rather than a wide dispersion of effort which might prove fruitless.

In England Now

A Running Commentary by Peripatetic Correspondents

EIGHT of us were shortlisted for the psychiatric job. We all turned up on the appointed day, greeted one another with artificial warmth, and then sat gloomily waiting to be called. The first candidate had just been summoned when there was a commotion outside the door and a healthy-looking extrovert burst into the room. "Thought I'd be late", he panted, throwing off his coat and smoothing his gleaming hair. Then he saw all of us for the first time clearly. His face showed his surprise. "What on earth are you all waiting for?" he asked. We looked at him in silence. No-one knew him and no-one liked to ask him his business. At length someone replied, "We're waiting for the interview."

The stranger became excited. "The interview", he cried several times. "All of you waiting for the interview? But I thought the job was fixed for me. Why have they asked so many to come here today?" We stared openmouthed at him, our hearts sinking, all of us suddenly conscious of his overwhelming right to the job. Indignantly he paced the floor and then he disappeared through the door. "Well, that's that", said the man in the corner, wiping away a tear. "We might as well go home." We nodded sadly at one another, the last vestiges of hope gone.

Five minutes later the stranger returned, his face wreathed in smiles. "You chaps gave me a shock. Why ever didn't you tell me you were psychiatrists? I'm up for the surgical job myself."

* * *

In the back of an old apothecary chest I recently found a letter dated July, 1895. It was from a fashionable London medical address and was sent to a patient in Chester. It read:

Dear Mrs. Fr——

Try the enclosed for a fortnight—if it fails I hardly know what else to suggest.

Yours sincerely

The enclosure was:

℞ Sodæ Nitriti gr. xii
Ammon. Brom. ℥ i
Aquæ ℥ vi
A sixth part twice a day after meals.

It has been said that the National Health Service has made doctors more honest. But what, Sir, could be more honest than that? Does it not conjure up the picture of a physician driven to his wits' end?

* * *

From a South Coast Consultant's postbag—"In 1955 while this man was living in London he had the misfortune to be sent to hospital on account of chronic bronchitis. By the time the big white chiefs had bronchoscoped him to exclude a neoplasm, repeatedly X-rayed his chest, barium-mealed him, given him tetracycline in the winter, and included him in a clinical trial, his confidence in his ability to live was shattered. He arrived here in 1959 and has been free of acute bronchitis ever since. However, he rarely ventures out, complains of persistent left-chest pain, and has driven his wife to electroconvulsion therapy. The fact that his chest is greatly improved since he left London does not reassure him. The pundits gave him the impression that he was very ill."

* * *

NEOLOGUE SPAWN—ONE UNIT *

Miss Wakeling pays a weekly call
Upon an Analyst
Because she often seems to fall
Into a kind of mist.
Her heart turns over like a ball,
Her kidneys sort of twist.

But yesterday, just after tea,
She tumbled down and brought to me
A funny looking wrist.
This time I think she'll have to see
A Somatiatrist.

* See this column, Nov. 25.

Letters to the Editor

THE CASUALTY DEPARTMENT

SIR,—In his very interesting Point of View (Nov. 25), Mr. Lamont paints a rather grim picture of the casualty department, and I feel he does both his own, and other, casualty officers less than justice.

Let me first say that the director he envisages of a casualty department, in addition to being qualified in industrial medicine and surgery, would have to be a master mind, who would eventually end up, as he says, "the ideal local deputy for the master neurosurgeon". Where shall we get the paragon of all these virtues? I can think of three people, eminent surgeons, who, with amalgamation together, would perhaps just touch on the fringe of this genius.

One of the ways that we have found of overcoming plunging the newly qualified doctor into casualty is to make it a senior post. Wherever does Mr. Lamont feel that these potential casualty officers are going to be instructed in the barbiturate poisoning, the clinically undiagnosable small rent in the instestinal tract, for it is certain that he will not see it at his teaching hospital? It is only at provincial casualty departments that the majority of these emergencies are seen, and here, no doubt, I will provoke a storm of abuse from the teaching hospitals.

I think also that the casualty officer would resent a "father" looking after him, and guarding him from the everyday buffeting and abuse that he is likely to meet. This, I feel, helps to mould the character of the young doctor and show him that to some extent he is the servant of the public, and also teach him to control any retort that he might like to make to the abusive patient.

Another and most important factor is that a lot of the tribulations of the casualty officer can be lessened by having adequate casualty staff. In the department to which I am attached, there are a junior hospital medical officer and four casualty officers who are house-surgeons to the orthopædic unit. In this way, adequate time has been allocated for duty in the casualty department and on the wards, each casualty officer being able to consult with his own consultant, or the one on official duty at any particular time.

If there is any fault to find, it lies, I feel, in the teaching hospitals. I have always been amazed at the young doctors' ignorance of the treatment of the cases they are most likely to meet in the casualty department. They all know the obscure conditions which crop up once in a lifetime, but none of them know how to reduce a Colles' fracture, how to put on a plaster, or even when a patient is dying.

We are very fortunate in this area, in that most of the factories are well staffed to cope with industrial injuries, even to the extent of X-raying their own minor casualties.

My own personal view of the proposal to have a director of accident services, in any hospital, is that it is the surest way to wreck the harmony which is so essential in any hospital between the consultants. I feel that if anybody is to direct an accident unit, it ought to be an orthopædic surgeon on the staff, who would do this job on an annual basis, and rotate with his colleagues.

Hove, Sussex. WALTER LAURENCE.

SIR,—As someone who has done a good deal of casualty work in his time, I agree with most of Mr. Lamont's points. I feel, however, I must take him up on his views about the industrial medical service.

An occupational health service has as its main objects the promotion of health among the employees and the protection of the employees as far as possible from any hazards of their occupation. Although we do a good deal of casualty work, it is not the object of an occupational health service to duplicate the treatment services provided by the N.H.S., and the scope of our

treatment is strictly limited to minor injuries and ailments, the criterion being roughly that the disability is not so great that it will prevent the patient continuing at work.

Mr. Lamont's takeover proposals would not, therefore, cover the main objects of an occupational health service, and even before he relieves us of the chore of doing our own casualties, he might care to examine his case a little more closely.

Of course cases are sent to the casualty department who could well have been treated in the works surgery, and the reasons may be social, political, or legal. Has Mr. Lamont never ordered an X-ray on grounds which are not purely medical? Of course, there are many small places of work whose first-aid facilities are disgracefully inadequate or non-existent, and many places of work without any form of occupational health service, and it is highly desirable that they should make good this deficiency. But in my own organisation, roughly approximating to the area of the Sheffield Regional Hospital Board, there were 22,302 attendances at the works surgeries last year, and out of these 178 cases were sent to hospital. These figures are significant even on a national level of 11 million casualties, and when it is considered that we are only one, and by no means the largest, of many occupational health services in this regional board area, the cost to the N.H.S. of absorbing the full care of these cases might be very high, and as a visit to a casualty department or doctor's surgery rarely takes less than 2 hours the cost to the men and the employers in lost productive time might be even higher.

Surely Mr. Lamont must admit that by referring less than 2% of the cases seen in our works surgeries we are doing something to screen the trivialities from the essential cases, and does he really think that under the present financial arrangements the N.H.S. is in any position to begin to cover the full treatment of all industrial injuries, when the general accident services of the country are already far below standard and urgently need large sums of money spent on them to bring them up to a reasonable level of efficiency?

East Midlands Gas Board,
Leicester.

A. R. BUCKLEY.

SIR,—I was delighted to read the article by Mr. Lamont and even more pleased to see a journal of such high repute give so much space to a full discussion of this problem.

It is noted that this memorandum was originally prepared for the Association of Hospital Management Committees. Eleven years ago, I wrote a similar memorandum circulated locally. In those days, however, the Cinderella of the casualty department was still left in her kitchen and the fairy godmothers from the Nuffield Foundation and the Government committees had not yet appeared to clothe her in respectability. The Handsome Prince has yet to be seen or else Mr. Lamont's article would not have been written. It is on hospital management committees that most of the blame for this sorry state of affairs still lies. Whilst they are content to appoint consultants to take charge of casualty departments on the absentee landlord basis, no improvement can be expected. We would all agree that the casualty department is not a clinic for the casual complaint. Too often such patients come to the hospital (1) because they are just passing, (2) because the general practitioner's surgery hours are inconvenient, and (3) because the doctor at weekends, half-days, and holidays is not available. If they are turned away because they are not considered to be casualties, a complaint from any source to the hospital management committee means a reproof to the casualty department on the principle that the customer is always right. Even in this hospital, which is probably more liberal than any in its provision of and support of the staff of the casualty department, such an attitude is not entirely dead. In the smaller hospitals where no senior staff are there to speak for the casualty department, the casualty officer takes the line of least resistance and treats these patients, and so the high proportion of casuals, mentioned by Mr. Lamont, will no doubt be reached. In this hospital, except at weekends and holidays, this figure never exceeds 5%. Regrettably, at holiday times a substantial minority of general practitioners do go away and expect the casualty department to look after their patients.

I agree with Mr. Lamont that it is high time that hospital management committees did appoint senior and experienced doctors to the casualty department, with full status and salary, who can by their example and teaching of the newly qualified raise the standard of work. I said by example because this senior man must be present in the department doing the work to set this example. This example cannot be set by a two or three minutes' visit to the casualty department several times a week. The hard-headed business and professional men who form the greater proportion of most hospital committees would not expect to run their own businesses and professions efficiently by casual brief visits. An increasing number of hospitals do appoint senior members of staff to take charge of casualty departments or a group of casualty departments. The majority of these are senior casualty officers of S.H.M.O. status with a nominal appointment of no longer than 4 years. To deny these people a permanent appointment and to deny them full consultant status seems rather a shabby method of evading the management committee's responsibilities. I agree with Mr. Lamont that the casualty service should have full status and that those gaining many years' experience in this work should be able to look forward to becoming consultants after this experience has been gained. In any other specialty some four to six years' work is required together with some years' experience in related posts. I think that posts in orthopædics, general surgery above preregistration level, and maybe general practice would be required in addition to several years in a casualty department, before a potential casualty consultant had had a wide enough experience to deserve the title of consultant. Such an aspiring consultant need not think that his experience will be wasted in casualty, for I can assure him that after many years' previous experience, I have found the last 12 years in this department have required all the intelligence, wit, skill, and experience previously obtained to be put to full use every day.

I express my thanks to Mr. Lamont for expressing his views so clearly and fully. I hope that the high-level committees considering at present this casualty dilemma, composed of people who have little recent experience of the day-to-day work in a casualty department, will take notice of the considered views of one who is in the thick of it.

The General Infirmary,
Leeds.

M. ELLIS.

SIR,—All who have direct experience of casualty work will have read Mr. Lamont's important memorandum with interest.

He classes at least 50% of new cases in the country's casualty departments as not needing hospital care. In our experience this number can be reduced to perhaps 10% by systematic but sympathetic explanations of the function of a casualty department to patients and occasionally to general practitioners. This remaining 10% can usually be dealt with very quickly and referred back to their doctors, although it sometimes has to be explained to them that the 999 magic carpet will not take them home again.

Mr. Lamont emphasises the need for the presence in every casualty department of a senior casualty officer—a father figure he so aptly terms it. No less important for an efficient 24-hour service is a team of good junior medical officers. Of the many skills required of them, fracture diagnosis, manipulative and plaster technique, and the immediate care of the severely injured are amongst the most important. At least half the work of a casualty department which sees mainly proper casualty patients is orthopædic. It is, therefore, to the orthopædic department that casualty should be related. Medical officers should attend or take part in follow-up fracture clinics, and at least be aware of the subsequent course of the severely injured, who have passed through their hands.

Given reasonable facilities, a casualty department can be a happy and rewarding place to work and will attract doctors of calibre, provided it is well organised.

The relationship between work on offer and the size of staff in the department must be well balanced, so that medical staff are neither rushed nor underemployed, and night and evening work must not be excessive. The night work must be shared by at least three medical officers in addition to the senior casualty officer, and this implies a casualty department which sees at least 25,000 new cases a year.

There are many casualty departments of strategic importance situated near main roads which will have a turnover of much less than 25,000, but where an efficient 24-hour service is no less important. In these the association with the orthopædic department could be much closer. There is no reason why the casualty officers should not work a varying proportion of their time as orthopædic house-surgeons, provided always that the needs of the casualty department take precedence.

South Devon and
East Cornwall Hospital,
Plymouth. K. G. PASCALL.

SIR,—It is always a pleasure to meet like minds, and Mr. Lamont's attempt to define the casualty dilemma in vivid terms may help to clarify a difficult situation.

The trend in administrative circles is to leave minor casualty work to the peripheral hospitals, and for major casualty work involving numbers of serious industrial and traffic accidents to be centralised in special accident units associated with general hospitals.[1] In these hospitals the traumatic surgeon and trauma teams will be fashioned in the manner pioneered at the Birmingham Accident Hospital. This will still leave a considerable number of vacancies to be filled by casualty officers well trained in the all-round techniques of resuscitation in accident and poisoning cases [2] as well as day-to-day problems described in Mr. Lamont's article.

Before we can hope for casualty work to become a branch of medicine on a par with other branches, however, it is of vital importance that a Casualty Charter is drawn up by the medical authorities concerned to define the conditions of work of casualty officers. There are far too many casualty departments where out-of-date equipment, lack of space, and poor staffing, together with impossibly long hours of work and lack of consultant supervision, cause good doctors to refuse to stay for any length of time.

If this hurdle of a Casualty Charter can be overcome, and security of tenure of appointment assured to casualty officers, it seems that graded apprenticeship is the next step in training a corps of casualty officers sufficient to bear the brunt of the service required. For the casualty department sprang from the need of the casual ward in times when overwhelming economic and personal disasters left number of good citizens in urgent need of help. The British public's compassionate instinct in this matter must still be treated with respect.

In order to enlist a devoted corps of casualty officers it is necessary to emphasise the special positive attributes required of them. For the casualty department is the advanced dressing-station on the battlefield of civilisation, and those of us who work in them know what a great privilege it is to be allowed to assist such large numbers of people in trouble.

I can think of no other branch of our professional work in which so constant a demand is made on our moral and physical capacities, and where the teamwork is carried out under such public scrutiny.

Watford and District
Peace Memorial Hospital,
Watford. H. R. CLAFF.

1. Accident Services of Great Britain and Ireland: Interim Report of Review Committee.
2. Central Health Service Council Report, December, 1960; paras. 41–49.

THE G.N.C. AND THE S.R.N.

SIR,—The General Nursing Council, as a result of their ruling that only hospitals of 300 beds can have a State-registered-nurse training school, have recently made proposals to withdraw recognition of the Wimbledon and Nelson Hospitals as a training school for State-registered nurses. In the opinion of the vast majority of medical men and women in this area this is a wrong decision, which will result in deterioration of the hospital services in the area. Unfortunately at the moment the decisions of the G.N.C. are not subject to any medical approval before implementation and it appears that, although they control only an ancillary service of medicine, they have the final and absolute say regarding the future of our hospitals.

We feel that this is a problem which may be presenting itself all over the country and causing grave concern to medical practitioners everywhere, both specialist and general, who work on the staffs of small hospitals. The policy of the G.N.C. has already been a factor in the serious falling-off in nursing recruitment and must inevitably lead to both reduction in the number of beds available for hospital cases, and a lowering of the standard of work done in these hospitals.

We feel that it is of the utmost importance that the decision of the G.N.C. in regard to this and other nurse-training schools should be reversed, or at least delayed, and we would be most grateful if the chairmen of medical staff committees of other hospitals who now find themselves in a similar predicament would communicate with the last of the undersigned at once so that a united effort can be made to preserve the Hospital Service.

C. P. PETCH
Chairman, Group Medical Advisory Committee, St. Helier Group Hospital Management Committee.
P. M. KELLY
B. W. WELLS
Chairman, Joint Medical Staff Committee Wimbledon and Nelson Hospitals.
Nelson Hospital,
Kingston Road, Merton,
London, S.W.20.

EPIDEMIOLOGY OF COMMON COLDS

SIR,—As Dr. Heald suggests (Nov. 25) your excellent leading article of Nov. 11 dealt almost exclusively with the epidemiology of the prodromal or virus stage of common colds. This is new, exciting, and highly important work, but it is not the whole story of the impact of these diseases upon the people, or their epidemiology in the wider sense. It leaves out of account the role of autogenous bacterial secondary infection, which, according to Ritchie's hypothesis, " bears a much larger share in the later disabling symptoms than has hitherto been supposed." [1 2]

The bulk of the loss of working time occasioned by colds and their grievous complications (sinusitis, bronchitis, pneumonia, and the like) seems to be associated with infection and invasion by the patient's own pharyngeal flora, activated as a result of the primary virus infection.

Although Dr. Heald is probably right in saying that Ritchie's investigations have not been *adequately* followed up, the picture is not so black as he makes out. If conclusions adverse to this hypothesis have been published I have either missed them or, like Dr. Heald, have regarded them as irrelevant. On the other hand, I know of several articles and other communications which have clearly supported Ritchie's hypothesis,[3–7] of which the most significant surely is that of McKerrow et al.[6]—a

1. Ritchie, J. M. *Lancet*, 1958, i, 618.
2. Ritchie, J. M. *ibid.* 1958, ii, 699.
3. Banks, H. S. *ibid.* p. 745.
4. Shulman, F. G. *ibid.* p. 1335.
5. *Hlth Bull. Edinb.* 1961, **19**, 12.
6. McKerrow, C. B., Oldham, P. D., Thomson, S. *Lancet*, 1961, i, 185.
7. Bateson, P. R., Allison, R. M. *Brit. J. clin. Pract.* 1961, **15**, 543.

report of a controlled clinical trial from the Pneumoconiosis Research Unit of the Medical Research Council. They concluded that "the weight of evidence now strongly supports the idea that recovery from the common cold can be speeded up by treatment with antibiotics (i.e., with a short course in the viral or prodromal stage). The most suitable antibiotic and the optimal dosage have not yet been determined". That, as I understand it, is how the matter now stands, and further elucidation is obviously required.

Leatherhead, Surrey. H. STANLEY BANKS.

DELIBERATE EMERGENCIES

SIR,—The Cranbrook Committee's recommendation that beds should be available for 70% of all confinements may be right for some parts of England, but it is certainly wrong for London. For a start, at least 70 pregnant women out of every 100 in London insist on having their babies in hospital, irrespective of need. Of the remaining 30 who would like to have their babies at home, many have unsuitable homes and most of the others are medically unsuitable—e.g., the grande multiparæ. The result is that beds have to be found for at least 90% of all pregnant women, and this figure will, I am sure, soon rise to 100%. In my opinion, this is as it should be. A woman should no more have her baby at home than she should have a dilatation and curettage on the kitchen table.

In your leader of Oct. 14 you urge that more beds should be provided; and there is no doubt that more beds are needed. But not so many as you suggest. We cannot expect that every pregnant woman should have a bed for her confinement *and* her lying-in; if she did, the number of maternity beds would be disproportionately large. Maternity is no doubt fashionable at the moment, but even so it should not take precedence over all other parts of the National Health Service.

I only have figures for my own area of London, but there at least we have enough consultant beds. The new ones should be general-practitioner beds—provided of course the general practitioners could be found to use them. They should be sited near, or in, a consultant unit, not only so that the consultant can exercise supervision but also so that the practitioner has access to ancillary services. Patients would be admitted to them for social rather than medical reasons, and antenatal care should be provided by a practitioner-obstetrician working in a clinic in the unit or a clinic provided by the local authority.

But if we are not to ask for beds to cover all confinements and all lying-in periods, then some mothers must be discharged from hospital soon after delivery. Provided the mother and her baby are fit and home circumstances are satisfactory, there is nothing against this. Moreover, a mother's wish to stay in hospital should not influence the doctor's decision. Every woman should, as a right, expect a bed from the National Health Service for her confinement, but not necessarily for her lying-in. After all, she is not ill.

Early discharge would allow greater use of beds, especially in the general-practitioner units where the patients would be normal. It would also mean that a higher proportion of labour wards must be provided, and (even more important) a much higher establishment of midwives. If the maternity services were put under one head, as many of us hoped the Cranbrook Committee would recommend, the system of early discharge would be easier to run, for there would be no dividing line between hospital and district midwives. Midwives would work in both on a rota, delivering in hospital for a time, looking after lying-in mothers at home for a time. This more elastic system would also probably reduce the shortage of midwives. Fewer would be lost to the service by marriage if we could give them work to suit their altered circumstances instead of forcing them to work under the old rigid regulations. Many married midwives with families might be willing to look after lying-in mothers in their homes. Nor need there be any break in the continuity of nursing care if the nurses, working both in hospital and on the district, were under the same head.

A service such as this would need the backing of an adequate and efficient home-help service—as has been shown in Holland. Home-helps are said to be hard to recruit; but perhaps this is again a matter of conditions of employment, especially financial.

I ask the Ministry of Health to consider these proposals urgently. The present state of affairs cannot continue without a breakdown. It takes time to build new beds, but planning should start at once. The general practitioners should consider whether they can use more beds, and I would ask them to consider their decision carefully. More beds will mean much extra work, for which, I would add, they should be paid. But they must not expect cover from resident medical officers, for there are not enough of these.

An overall maternity nursing service such as I have suggested should be organised immediately, so that the beds we have can be used to greater effect. The increasing numbers of confinements will not wait upon the completion of new beds, but an integrated midwifery service would at once make possible the introduction of a system of early discharge and home lying-in where medically and socially suitable.

My suggestions are made with London in mind; for I do not know conditions in other parts of England. But I think it probable that the whole country will in the end need such an organisation; indeed some areas already have it and it is working well.

London, W.1. G. W. GARLAND.

COLLES' FRACTURE

SIR,—I read with interest and some astonishment your annotation of Oct. 28. In my experience, the use of Steinmann's pins and plaster, as you advise, has never been necessary, and the results of any pin-track sepsis, with so many tendons related to the lower fragment, hardly need be emphasised.

There seem to be three types of these fractures:

(*a*) In the age-group 20–40: a good reduction is obtained and held until the fracture is united, and a good result is the rule.

(*b*) In the age-group 40–60: such fractures are often comminuted and the dorsal surface of the radius is crushed. A good initial reduction is easily obtained but tends to slip because of the "missing bone". If a remanipulation is carried out after 2–3 weeks, the reduction can be held and a good result obtained. Finger and shoulder exercises are important.

(*c*) 60 and over: the same applies as in (*b*) except in the senile patient, when no special efforts are justifiable. Many ladies of 70–80 live alone, do their own housework, and need a good wrist if they are to remain independent.

It may be argued that two anæsthetics and manipulations are unjustified for such an injury, but I submit that such trouble is worth while: it is certainly safer than pin and plaster. In all cases too much importance cannot be attached to immobilising the wrist in full ulnar deviation, as emphasised by L. W. Plewes in *Recent Advances in Surgery* (1961).

Newcastle upon Tyne. J. F. STONE.

NON-CONSUMMATION OF MARRIAGE

SIR,—I read with great interest the article by Dr. Dawkins and Dr. Taylor (Nov. 4). This marital difficulty has presented in a clinic dealing largely with problems of frigidity referred from other psychiatrists of this hospital. Up to the present, 33 examples have been treated.

While endorsing many of the findings and much of the treatment of Dr. Dawkins and Dr. Taylor, I have adopted a combination of psychotherapeutic and physical methods, aimed at achieving mutual orgastic satisfaction in the marriage partners, rather than merely the relief of non-consummation. The results so far suggest that the application of these two diverse methods by the one therapist is advantageous.

This sexual difficulty seems to necessitate seeing the partners both separately and together, when it soon becomes clear which is the one most in need of treatment—commonly it is the wife. Hence I have adopted the psychotherapeutic technique described by Abraham [1] and I also use physical treatments, often involving dilators, aimed at the deconditioning of vaginismus. In no instance have hymenectomy or dilation under an anæsthetic been necessary. In fact, where patients have already had this form of surgical treatment and it has failed, they require notably longer treatment for success.

Physical examination has never been attempted at the first interview, but only after rapport and confidence and a degree of insight have been gained. Moreover, at the outset of treatment, both partners are given to understand that no attempts at intercourse shall be made until painless consummation is considered to be possible by both husband and wife. When this stage has been reached, I find it important to solve the added problem of contraception, as part of the integrated treatment, so that sexual satisfaction may be well established before conception is planned.

Of the 33 cases treated, consummation was achieved in 31. The degree of sexual satisfaction varied from vaginal orgasm in 20 patients to clitoral orgasm in the remainder.

The Maudsley Hospital,
London, S.E.5. CARICE ELLISON.

ADVERTISEMENTS FOR HEALTH

SIR,—We agree with Mr. Stocker (Oct. 14) that sorbitol sweets are harmless to the teeth and may in fact be beneficial. He is completely wrong, however, in his assertion that sorbitol itself would be at least as effective as a salivary stimulant as the tablet described by us,[2] which contains other stimulatory ingredients.

Sorbitol itself is a relatively poor salivary stimulant and it is used in the tablet mainly as a non-fermentable carrier for the malic acid which is the active ingredient. Organic acids, such as malic acid, are (weight for weight) between 10 and 100 times as effective as sorbitol as salivary stimulants.

An experiment was carried out in which various amounts of malic acid were incorporated in tablets of sorbitol. The tablets were sucked by eight subjects; the average amount of saliva produced by the tablet was as follows:

Percentage of malic acid in tablet	*Saliva stimulated (g.)*	*Rate of salivary stimulation (g. per min.)*
0 ..	13·9 ..	2·6
2 ..	19·9 ..	3·9
4 ..	22·8 ..	4·6
6 ..	25·3 ..	5·3
8 ..	25·9 ..	5·1
10 ..	28·7 ..	5·9
Difference required for significance ($P = 0·05$) ..	1·1 ..	0·25

A tablet containing 6% malic acid produced nearly twice as much saliva as a tablet containing no acid. We have shown that the tooth-cleansing effect of tablets of this kind is proportional to the amount of saliva stimulated.[2]

We would not agree with Mr. Stocker in recommending ad-lib consumption of sorbitol sweets. These, like apples, are beneficial when taken in moderation, but a surfeit can be as uncomfortable as a surfeit of apples.[3]

Unilever Research Laboratory,
Isleworth, Middlesex. R. CLARK.
D. I. HAY
C. J. SCHRAM
Unilever Research Laboratory,
Sharnbrook, Bedford. B. J. WAGG.

1. Abraham, H. *Brit. med. J.* 1956, i. 837.
2. Clark, R., Hay, D. I., Schram, C. J., Wagg, B. J. *Brit. dent. J.* 1961, **111**, 244.

LONG-TERM ANTICOAGULANT THERAPY

SIR,—Dr. McFarland's remarks in his letter of Oct. 14 deserve wide dissemination, and he has earned at least my gratitude for his courage in saying what many of us have undoubtedly felt for a long time. I make particular reference to his second paragraph where he says: "A more sensible alternative would be not to start this treatment in the first place . . . The realisation that discontinuing this therapy may be more harmful than not starting it in the first place should be disconcerting to the enthusiasts."

Asbury Park,
New Jersey. VICTOR KNAPP.

HEATING—VENTILATING—COOLING

SIR,—With Mr. Constable (Nov. 25), we congratulate Professor Wells on his succinct summary of the problems and trends in the ventilation of operation-theatres. But some of Mr. Constable's comments are questionable. He rightly says that downward-displacement ("piston") ventilation is not universally accepted, and mentions the advantages of a high-velocity turbulent system. But in making the comparison, Mr. Constable has quoted only disadvantages of the one system and advantages of the other. Surgeons will need more information than this to help them choose the type of ventilation they prefer.

The fundamental characteristic of a displacement system is that it carries airborne bacteria from their point of liberation to the nearest air-outlet port by a relatively direct route, thus getting them out of the room in the shortest possible time. Turbulence takes longer to get the organisms out of the room but, in the process of removing them, quickly reduces their concentration close to the point of liberation by dispersing them throughout the room.

The dispersing effect of turbulent ventilation is an advantage when organisms are shed from a source above and very close to the wound, but is clearly a disadvantage when the source is further away. Studying bacterial contamination of the wound area in an experimental operation-theatre, we found [4] that when organisms were liberated in the position of the surgeon's head, displacement ventilation allowed about twice as much contamination as the turbulent system. But when bacteria were liberated from the position of the surgeon's lower trunk, from the floor, or from the periphery of the theatre, the dispersing effect of the turbulent ventilation brought organisms into the wound area and caused contamination varying from 5 to 100 times that from the displacement system.

It would be unwise to choose turbulent ventilation for its performance in one particular circumstance and to ignore its performance in others which, according to present knowledge, seem more likely to occur. For, as far as staphylococci are concerned, the evidence is that they are shed from the skin and clothes and are raised from the floor more profusely by persons who are walking about than by those who are still; that very few escape from the nose and mouth of an unmasked and virtually none from a masked person [5 6]; and that people who are dispersers of staphylococci tend to shed profusely from the lower parts of the body.[7] It thus seems that airborne

3. Peters, R., Lock, R. H. *Brit. med. J.* 1958, ii, 677.
4. Blowers, R., Crew, B. *J. Hyg., Camb.* 1960, **58**, 427.
5. Duguid, J. P., Wallace, A. T. *Lancet*, 1948, ii, 845.
6. Shooter, R. A., Smith, M. A., Hunter, C. J. W. *Brit. J. Surg.* 1959, **47**, 246.
7. Hare, R., Thomas, C. G. A. *Brit. med. J.* 1956, ii, 840.

staphylococci are more likely to come from the relatively mobile nurses at the periphery of the room than from the surgeon who, in any case, is likely to shed his staphylococci below rather than above the operating-table. On balance, therefore, displacement ventilation seems to offer greater protection to the patient than does the higher-velocity turbulent system advocated by Mr. Constable.

On grounds of comfort, too, the choice depends on more than the one point mentioned by Mr. Constable. In fact, the lower air velocity of a displacement system does not " cause considerable discomfort to the staff ". It is more than compensated by the fact that, even without refrigeration, displacement ventilation keeps the room-temperature and possibly the humidity appreciably lower than does the turbulent system. Opinions on these comfort problems are often based on theoretical considerations rather than on observations in comparable theatres ventilated at the same rate of airflow by each of the systems. There are many theatres of each type in this region, and there is not the slightest doubt that those with displacement ventilation are the more comfortable. When refrigeration is available, the comfort conditions offered by the two systems are identical and the choice between them then depends only on their bacteriological performances.

Lastly, we should like to correct the oft-repeated statement that displacement ventilation cannot be maintained when there is much movement in the room and when cooled air is being introduced. The displacement effect is certainly reduced under these circumstances; but, even so, the performance of a displacement system in removing bacteria is appreciably better than that of a turbulent system.

Turbulent ventilation is certainly cheaper and calls for less precise engineering design than displacement ventilation, but these advantages should not be allowed absolute precedence over matters of safety and comfort.

Public Health Laboratory,
General Hospital,
Middlesbrough.

ROBERT BLOWERS
BERYL CREW.

DIAGNOSIS OF ACUTE APPENDICITIS

SIR,—I should like to support Mr. Knight's condemnation (Nov. 18) of the statement that there is never an acute appendicitis present when cæcal gurgling can be elicited.

I have recently seen two cases of acute appendicitis both of which had definite cæcal gurgling and minimal other abdominal signs. Both cases were in children, with rather vague abdominal and general symptoms. However, rectal examination in both cases elicited definite tenderness and increased temperature on the right side. At appendicectomy, both patients had the enlarged voluminous mobile type of cæcum with a much elongated appendix hanging over the brim of the pelvis. Both appendices appeared normal in their proximal portions but their terminations in the pelvis were acutely inflamed and pregangrenous.

St. Bartholomew's Hospital,
Rochester, Kent.

MITCHELL J. NOTARAS.

DOCTORS FOR THE FORCES

SIR,—It is no use Dr. Whitty (Nov. 25) declaring what ought to be done to form a Combined Forces Medical Service while volunteers provide the manpower.

I have served just on twenty-seven years either as a Naval reservist or as a regular because it was what I wanted to do. The same sentiments have moved my colleagues to choose the Army or the Royal Air Force. We opted for the service we wanted. It does not necessarily follow that we would volunteer *at all* for a combined service which would take us away from our ships or planes or field hospital.

In any case it is not the organisation of the specialties or even of hospitals as a whole which governs the needs of the medical services of the Armed Forces: it is the general-duty staff who have to get things done by knowing the inner workings of their own Service in detail.

It is possible that I am in closer practical touch than Dr. Whitty with the problems of nuclear war. In an episode of that nature the R.A.M.C. would act as a mobile auxiliary to the National Health Service: it is unlikely that the Royal Navy or R.A.F. will be involved in the same way except in the direct vicinity of Service units or towns.

Brighton.

W. S. PARKER
Medical Officer of Health.

CHORIONIC GONADOTROPHIN IN THE OBESE

SIR,—Simeons [1] and Lebon [2] have reported enthusiastically on the effect of daily injections of 125 I.U. of chorionic gonadotrophin coupled with a fat-free 500-calorie diet for weight reduction. Both workers imply this procedure is always effective. I have used this method over the past two years in 42 patients. In spite of the shortcomings, and the unknown mechanisms involved, I continue to find this procedure a useful tool in some obese patients.

A total of 42 patients (14 male, 28 female) began 69 courses of injections, but only 45 courses of 20 or more injections were completed (i.e., 24 courses failed according to the criteria of Simeons, although 8 of these were considered by the patients themselves to be successful and were discontinued because the patient had reached a satisfactory weight). The rest were discontinued for a variety of reasons, the main underlying one being that the patient could not stand the strain of the diet. Even in 14 of the courses of more than 20 injections appetite-depressant tablets (usually 'Tenuate', diethylpropion HCl) were needed by the patient in order to maintain the diet. This appears to be at variance with Simeons' findings that " under the peculiar effect of gonadotrophin the obese person could continue this diet for several weeks without the least discomfort ".[3]

During the regime the phenomenon of " sticking " was observed in 6 of the courses of 20 or more injections and in 5 of those having less. By " sticking ", I mean maintenance of the same weight for more than 7 days despite the continuance of the diet. This occurred more commonly in women than in men (9 : 2) and was usually premenstrual. However, the demoralising effect of keeping to a strict diet and seeing no results, especially during this notoriously emotionally labile time, was sufficiently strong for the course to be terminated in 5 patients. Only 1 of the " sticking " patients was found to be hypothyroid, but the others were physically normal.

The results of the regime in the 20+ courses was an average less of 0·59 lb. per day in the males and 0·34 lb. per day in the females. In the courses of less than 20 injections the respective figures were 0·37 and 0·42. Only the first male figure compares with Simeons' 0·5–1·0 lb. per day and does not come near Mr. Lebon's figure of 0·7–0·8 lb. per day.

Further doubt about the value of the chorionic gonadotrophin has been expressed by Sohar [4] who kept a group of patients on a similar regime with daily saline injections for some and gonadotrophin for others. He reports 6 failures, 5 of which were given gonadotrophin. His criterion for " failure " was a loss of less than 150 g. per day (0·33 lb.), not the abandoning of the regime. These failures would be comparable to my " sticking " patients. The cause of this phenomenon remains obscure.

Nevertheless, it is clear that the daily routine of seeing the doctor, having an injection, and being weighed are together often highly effective in a condition heavily loaded with psychological factors. Further research is needed in at least two directions: (1) a double-blind control to test the value of chorionic gonadotrophin against

1. *Lancet*, 1954, ii, 946.
2. *ibid.* July 29, 1961, p. 268.
3. *J. Amer. geriat. Soc.* January, 1956, p. 37.
4. *Amer. J. clin. Nutr.* 1959, **7**, 514.

saline injections; and (2) the use of the daily weighing regime by the doctor *without* injections to see how much the results are due to the close supervision and encouragement.

London, S.W.1. M. A. KALINA.

*** The use of chorionic gonadotrophin in the treatment of obesity is also discussed in an article by Dr. Carne on p. 1282.—ED. L.

HALOTHANE

SIR,—Your leading article of Nov. 18 deserves great praise, both for its succinct account of the present position of halothane and for its fairness in presenting the published facts.

For more than 4½ years, halothane/oxygen given with spontaneous respiration has been the routine anæsthetic in the North Down Hospitals Group. A large series of cases has been recorded which includes all the common operations of general surgery, orthopædics, pædiatrics, midwifery and gynæcology, E.N.T. surgery, and ophthalmology. More than 12,000 cases have been anæsthetised by a modification [1] of the closed-circuit method described by Marrett.[2] In the light of the experience so gained we should like to comment on some of the points in your leader:

(1) "*. . . there is frequent comment in hospital committees about its cost.*"

This comment is more than justified when it is remembered that the use of halothane to supplement an 8-litre flow of N_2O/O_2 multiplies eightfold the cost of anæsthesia per hour. At least 75% of the halothane consumed is spilled into the surrounding atmosphere without making any contribution to anæsthesia.

Few anæsthetists would favour a similar method of using cyclopropane, which is the only other anæsthetic agent of comparable costliness. Closed-circuit anæsthesia, whether with an extrinsic or intrinsic vaporiser, enables halothane/oxygen to compete economically on almost equal terms with the combined relaxant sequence.

(2) "*Adrenaline should never be injected without good cause into the patient under halothane.*"

We have anæsthetised with halothane more than 300 patients undergoing anterior colporrhaphies and posterior colpoperineorrhaphies. In each case the surgeon injected at least 20 ml. of 1/120,000 adrenaline into the operation field to assist hæmostasis. No significant cardiac irregularities were detected clinically, and many of these patients were monitored electrocardiographically with negative results. The potential danger lies in accidental intravenous injection of adrenaline, which can be avoided if the surgeon inserts the full length of his needle and injects only as it is being withdrawn.

(3) "*It does not, however, produce abdominal relaxation comparable with that obtainable with ether or chloroform.*"

This statement is true only of light halothane narcosis. In the profound anæsthesia obtainable by the V.I.C. closed-circuit method, an extremely flaccid abdominal wall is produced. Our surgeons perform complete and partial gastrectomies, vagotomies, bile-duct explorations, and cholecystectomies without demanding the use of relaxants.

Carbon-dioxide retention resulting from minute volumes of 3 litres or less has little harmful effect, particularly if atropine premedication is omitted. Cardiac irregularities or increased capillary oozing, the only signs occasionally noticeable, are easily abolished by switching off the vaporiser, flushing the circuit with pure oxygen, and assisting respiration for a few minutes to allow the soda-lime to absorb the excess CO_2.

(4) "*It relaxes the parturient uterus; and therefore its use in operative obstetrics, where there is a risk of postpartum hæmorrhage, is dangerous. It passes across the placental barrier to the fœtus and depresses its respiratory centre significantly; for this reason its administration immediately before delivery may also be undesirable.*"

Halothane is undoubtedly a very potent uterine relaxant. This action, however, becomes dangerous only if anæsthesia is maintained at an unnecessarily deep level.

In a series of over 120 successive lower-segment cæsarean sections anæsthesia with light halothane/oxygen without intravenous barbiturates or relaxants produced no case of failure of the uterus to contract and retract. We make it a rule to inject intravenously 1 mg. of ergometrine maleate as soon as the fœtal head has been extracted from the uterine wound.

For forceps deliveries and breech extractions we use a halothane-air drawover technique previously described,[3] the vaporiser being a modified Marrett's trichlorethylene bottle. Anæsthesia is kept light enough for the patient to phonate slightly during painful manipulations but deep enough to avoid reflex movements. The mask is removed as the head is being delivered, and 1 mg. ergometrine maleate is then injected intravenously. No further anæsthetic is given unless the patient moves during any necessary suturing. In more than 300 cases there has been no increased incidence of postpartum hæmorrhage or retained placenta.

As regards fœtal respiratory depression, neither after cæsarean section nor after vaginal delivery have we noticed any greater difficulty in resuscitation than when conventional anæsthetic methods were used.

The obstetricians with whom we work are quite happy with both the maternal and neonatal aspects of halothane anæsthesia. They are especially impressed by the almost complete absence of vomiting during both induction of and recovery from obstetric anæsthesia.

Ards Hospital, Newtownards, Northern Ireland. M. A. WOODS
T. A. BROWN.

SIR,—Dr. Hewer's letter of Nov. 25 poses an interesting question. It has always puzzled me that some leading workers with halothane should continue to advocate its use with higher than atmospheric oxygen tensions and spontaneous respiration (not less than 50% oxygen is recommended in one current textbook). There seems no clear reason for this unless it symbolises a hostage to Fortune, with the admission that the patient is under-ventilating.

In this "scientific" era, far removed from 1934 and the mysteries of cyclopropane "shock", it seems wrong that the injustice to patients of subjecting them to respiratory depression—and the inevitable accompanying carbon-dioxide retention—should still be furthered by "correction" with oxygen-rich mixtures.

Cyanosis, we have all been taught, is an unreliable sign of hypoxia (and hence here hypoventilation); but at least it can be elicited, cost free, in the vast majority of patients, by all who practise anæsthesia and will but use near-atmospheric oxygen tensions.

The cutaneous vasodilatation produced by halothane should make cyanosis easy to recognise, and notably significant if it occurs despite the lowered oxygen consumption which halothane produces.[4–6] Perhaps the main current disadvantage of cyanosis as a sign is that it needs only basic physiological, as opposed to expensive man-made, apparatus to elicit—one's eyes, plus the readiness to observe.

Surely if even half our patients were so anæmic as to fail to show cyanosis, we could be doing good by allowing ourselves to recognise its significance in the remainder? The practice of using oxygen-rich mixtures with halothane denies this remainder, except almost terminally, the chance of giving a warning sign, without conferring in exchange any but spurious protection. This technique is surely rather like the ostrich's approach to danger.

1. Brown, T. A., Woods, M. A. *Brit. J. Anæsth.* 1958, **30**, 333.
2. Marrett, H. R. *Brit. med. J.* 1957, ii, 331.
3. Woods, M. A., Brown, T. A. *Brit. J. Anæsth.* 1959, **31**, 321.
4. Severinghaus, J. W., Cullen, S. C. *Anesthesiology*, 1958, **19**, 165.
5. Orton, R. H. *Med. J. Aust.* 1958, i, 830.
6. Nunn, J. F., Matthews, R. L. *Brit. J. Anæsth.* 1959, **31**, 330.

Should not the standard practice for halothane administration by spontaneous respiration be with little more than 20% oxygen? Cyanosis of any degree in these circumstances demands immediate reduction in halothane concentration and the institution of assisted or controlled respiration. As I see it, high oxygen tensions are plausibly permissible in controlled respiration alone, and even then only when the now well-recognised risks of halothane overdosage are kept well in mind.

Exeter. P. BUTLER.

TREATMENT OF EJACULATIO PRÆCOX WITH MONOAMINE-OXIDASE INHIBITORS

SIR,—Premature ejaculation, occurring before or very shortly after penetration, can be a grave cause of marital disharmony and distress, and reports on its treatment seem generally inconclusive.

The method described here resulted from the observation of Selikoff and Robitzek [1] that when depression was treated with monoamine-oxidase-inhibiting drugs one of the side-effects, after a month or more, might be delay in ejaculation followed sometimes by impotence if high dosage was continued. After I began to try the drug as a means of treating ejaculatio præcox, I found that Santanelli [2] had given iproniazid for "seminal dyskinesia", and had obtained improvement in 38 out of 40 cases of premature ejaculation. Treatment had lasted two months and the cases had been followed only for a further month.

Iproniazid ('Marsilid') was the drug I used first (50 mg. daily or twice daily). In the 2 cases treated control of ejaculation was satisfactory. When doubts about the safety of iproniazid were raised, isocarboxazid ('Marplan') was substituted.

The first patient (A), who had been controlled with iproniazid 50 mg. b.d., was given isocarboxazid 10 mg. t.d.s., but the dose had to be raised to 10 mg. q.d.s. The second patient (B) was given isocarboxazid 10 mg. b.d., while the third (C), who had not had iproniazid, was started on isocarboxazid 10 mg. t.d.s. In each case the tendency to premature ejaculation was controlled in six weeks and some improvement was noted in three. Patient B complained of slight delay in micturition on iproniazid, and patient C noted mild constipation on isocarboxazid. In no case did failure of erection or impotence develop, and patient C later said "I can hold ejaculation for any length of time." If treatment was discontinued, the symptom reappeared less than two weeks after the last dose of the drug.

These 3 patients have now been under treatment for a year, and 3 others have been treated on the same lines with almost equally satisfactory results:

One patient, for the whole ten years of his married life, had suffered from ejaculation before penetration, and he came for treatment because of depression. His improvement has been slower than that of the others; moreover, it has been harder to balance the dose. Isocarboxazid 10 mg. t.d.s. failed to delay ejaculation, while 10 mg. q.d.s. at first caused impotence. More recently he has been able to take 10 mg. q.d.s. and maintain an erection. He has needed much reassurance to allay his deep-rooted feeling of sexual inadequacy.

The other 2 patients, one with precipitate and the other with accelerated ejaculation, came at the instigation of their wives. Both the wives and the patients are satisfied with the results of treatment for six months.

The dosage must be adjusted for each patient and treatment must be continuous. Patients seem reluctant at first to accept the idea of continuous treatment, and the first 2 discontinued the drug; but they quickly asked for it to be started again.

1. Selikoff, I. J., Robitzek, E. H. *Dis. Chest*, 1952, **21**, 385.
2. Santanelli, R. Le sindromi depressive. Turin, 1960.

That monoamine-oxidase inhibitors slow ejaculation by interfering with conduction in the sympathetic nervous system is supported by the findings of Gertner.[3] Perfusing the superior cervical ganglion of the cat with a solution containing iproniazid, he found that ganglionic transmission was blocked and that the degree of block depended on the concentration of iproniazid in the perfusing fluid. In low concentrations the inhibitors cause the block to develop gradually, but the effect increases with time. Using iproniazid, Kamijo et al.[4] found that similar effects on the isolated rabbit uterus and isolated rat seminal vesicle were completely reversible.

With the doses we used, the patient had no swelling of the ankles or marked increase in weight. Nor was there any striking change of mood, other than the relief occasioned by removal of the disability.

Since treatment may have to be continued indefinitely, it is essential to use a monoamine-oxidase inhibitor which has no toxic effects in the doses given. Isocarboxazid 20–40 mg. daily seems satisfactory.

I am indebted to Dr. S. G. Bayliss, clinical research assistant, Roche Products Ltd., and Dr. Lorna Wing for their helpful advice and criticisms.

Netherne Hospital, Coulsdon, Surrey. DOUGLAS BENNETT.

PRISON DOCTORS

SIR,—Dr. Kidd's letter (Nov. 25) and your leader (Oct. 7) refer to several reasons why the Prison Medical Service is isolated, understaffed, and unattractive. May an onlooker suggest that an even more important reason may be that many, perhaps most, doctors fight shy of a Service in which their patients may include a man or woman under sentence of death? The doctor may even be required to use his skill so as to ensure that his patient shall survive until execution.

Hanging is the antithesis of therapeutics, and when Britain follows the example of more civilised countries and abolishes the death penalty, there will be a better chance of prisons turning into the therapeutic communities which you desire.

London, S.E.5. FRANK BYROM.

DISCS, LESIONS, AND SYNDROMES

SIR,—Dr. Dalgleish (Nov. 11) seems to accept the view that visceral symptoms may be caused by mechanical or pathological interference with the function of the intervertebral joint complex, and postulates a reflex mechanism for this. He suggests his hypothesis provides a definition for the osteopathic lesion.

Far from suffering from lack of definition, this term has been the subject of too many definitions, many of them vague and confusing. The definition we use today is deliberately confined to describing the clinical entity we are called upon to treat.[5] Dr. Dalgleish's hypothesis, however, is not new. In 1935 MacDonald and Hargrave-Wilson [6] postulated the existence of reflex visceral disturbances as a result of afferent stimuli arising in the structures of the abnormal intervertebral joint. Samson Wright [7] and Fulton [8] both suggest that afferent impulses of somatic origin can and do initiate, within the spinal cord, efferent impulses which influence the function of structures under autonomic control. The ear-cough reflex and the fatal syncope reported after ear syringing of patients with heart-disease are examples of such a "somatico-visceral reflex".

3. Gertner, S. B. *Nature, Lond.* 1959, **183**, 750.
4. Kamijo, K., Koelle, G. B., Wagner, H. H. *J. Pharmacol.* 1956, **117**, 213.
5. Stoddard, A. A Manual of Osteopathic Technique; p. 22. London, 1959.
6. MacDonald, G., Hargrave Wilson, W. The Osteopathic Lesion; p. 46. London, 1935.
7. Wright, S. Applied Physiology; p. 765. London, 1952.
8. Fulton, J. F. Physiology of the Nervous System; p. 204. London, 1949.

It may be argued that, while physiologists accept such a reflex in principle, a strain or similar lesion of an apophyseal joint would not stimulate impulses of sufficient strength to initiate such a reflex. Feinstein et al.[9] injected saline into paravertebral muscles and into the intervertebral articulations from the occipito-atlantal joint down to the sacrum. In addition to observing the territories of reflex pain radiation, they noted autonomic reflex features such as bradycardia and fall in blood-pressure. Such a reflex mechanism may also explain the results obtained in renal colic and dysmenorrhœa by cooling the skin innervated by the related neural segments.[10]

Romford, Essex. C. I. DOVE.

HOOKWORM ANÆMIA IN COLOURED IMMIGRANTS

SIR,—In 1959 over 15,000 immigrants from the West Indies, Bermuda, India, Pakistan, and Ceylon entered this country.[11] In our part of London, the statement in *Modern Trends in Gastroenterology* (1952) that helminthic disease has become comparatively uncommon in Great Britain is no longer true. In the past 6 months we have seen six coloured patients with hookworm, of whom five were anæmic. A patient with a hæmoglobin of 4·7 g. per 100 ml. (32%) was sent to the outpatient department for investigation with his anæmia unrecognised; and a patient with effort angina was treated with glyceryl trinitrite when his hæmoglobin was 4·1 g. per 100 ml. (28%).

In view of this difficulty in recognising severe anæmia in coloured people, our experience may be of interest.

All the patients detailed in the accompanying table had originally lived or worked on farms. All had multiple worm infestations (hookworm, whipworm, roundworm). Social status determines what work the patient is able to get in England, and hence the quality of his diet. Woodruff[12] states that moderately heavy hookworm infestation is well tolerated by a well-fed patient. It seems probable that case 6 was seen before she had become anæmic, although none of our patients admitted that their diet was inadequate.

We have all certainly missed anæmia even in white patients, and the darker the skin the more readily is this mistake made. In a healthy Negro, a warm red glow is apparent beneath the dark colour, but in an anæmic dark-skinned person close scrutiny reveals a striking pallor under the pigment. Once this " pale shade of black " has been appreciated, severe anæmia in coloured folk need not go untreated.

We thank Dr. Horace Joules and Dr. Keith Ball for allowing us to describe their patients.

Central Middlesex Hospital, London, N.W.10. I. W. GLICK A. E. STEVENS.

9. Feinstein, B., Langdon, J. N. K., Jameson, R. M., Schiller, F. *J. Bone Jt Surg.* 1954, **36A**, 981.
10. Ellis, M. *Brit. med. J.* 1961, i, 250.
11. *Whittaker's Almanack*, 1961.
12. Woodruff, A. W. *Brit. med. J.* 1952, ii, 988.

SIX PATIENTS WITH HOOKWORM ANÆMIA

Case	Sex	Age	Origin	Time in England (mos.)	Presenting symptoms	Hb (g. per 100 ml.)	Eosinophils	Comment
1	F	30	India (Calcutta)	9	Headache, sore throat, fever, cough	7·5 (*51%*)	46%	Presenting symptoms possibly due to upper-respiratory-tract infection. Anæmia not recognised clinically on admission
2	F	27	West Indies (St. Lucia)	12	Abdominal pain, melæna	7·5 (*51%*)	26%	Melæna drew attention to anæmia
3	M	41	West Indies (Grenada)	4	Effort dyspnœa and angina, black bowel motions	4·1 (*28%*)	24%	Anæmia not recognised clinically before admission; treated with glyceryl trinitrite
4	M	34	West Indies (St. Lucia)	12	Palpitation, intermittent claudication	5·0 (*34%*)	13%	Sent to outpatient department for cardiac investigation. Anæmia unrecognised
5 (Brother of case 4)	M	31	West Indies (St. Lucia)	13	Abdominal discomfort, palpitation, intermittent claudication	4·7 (*32%*)	..	Brother (case 4) made diagnosis and sent him to casualty department
6 (Wife of case 4)	F	29	West Indies (St. Lucia)	3	No symptoms	12·7 (*86%*)	12%	Sent for and admitted in view of family history

A TECHNIQUE FOR NUCLEAR SEXING

SIR,—The technique described below for determining nuclear chromatin patterns in oral smears enables screening of up to 120 individuals a day. Smears may be rapidly collected on wards and then read in the laboratory.

Clean pre-coded glass microscope slides are smeared with firm scrapings of the buccal mucosa obtained on the edge of a 3-inch flexible stainless-steel spatula. The scrapings are flattened and spread with a second slide, the slides being pressed together with the fingers to distribute the scrapings in a thin layer. The smear is made by slipping the slides apart lengthwise, it being possible, with practice, to leave most of the material on the desired slide.

The slide is placed in a Coplin jar of ether / alcohol (1 / 1) until read, or it may be removed after half an hour's fixation and dried. The slide, either dried or wet with fixative, is stained with a drop of 1% natural orcein in 45% acetic acid, a coverslip is placed over it, and excess stain is pressed out on a tissue. It may be examined immediately, though staining of nuclei in the centre of cell masses requires about 5 minutes. Staining and reading is conveniently done in batches of 10 slides.

Stained nuclei in sheets of cells in which the cytoplasm and cell membranes are not stained are selected under low power for analysis. Rapid definitive reading of a smear requires such material to be present. The oil-immersion objective is always used in examination of individual nuclei for the sex-chromatin body, and a material in at least two areas of the slide is examined before a decision is made.

If it is desired to make a slide permanent, the coverslip is floated off in 45% acetic acid. The slide is then rinsed drop-wise with 45% acetic acid until dye does not appear in the runoff, air dried, flooded with xylol, drained, and mounted in a xylol solution of resin under either the same or a new coverslip.

Experience with over 1500 smears using this method compared with over 2000 smears using the cresyl-echt-violet staining method of Moore and Barr [1] indicates the following advantages:

(*a*) The proportion of smears unsuitable for analysis because of material lost during fixation and staining is greatly reduced.

(*b*) Elimination of the hydrating, staining, and dehydrating baths saves much processing time and material.

(*c*) Aceto-orcein appears to give better identification of the sex-chromatin body and less variation among batches of dye.

(*d*) Aceto-orcein staining is satisfactory on slides handled by:
(1) Fixation in ether: alcohol or 95% alcohol only, followed by air drying and staining.
(2) Air drying followed by ether/alcohol fixation and staining.

1. Moore, K. L., Barr, M. L. *Lancet*, 1955, ii, 57.

(3) Air drying then staining without other fixation.
(4) Direct staining of the fresh smear (Sanderson [2]).

In my experience, rapid and definite reading of smears is facilitated by removal of fatty materials by the ether/alcohol fixation, and this procedure is preferred. Use of this technique has confirmed Sanderson's observation of a nuclear body in cells from males. This body is a third to a half the diameter of the usual sex-chromatin body, with the same intense staining, often with a narrow clear halo, located on the nuclear membrane and occurring in about 10% of smears from human males. It may appear in up to 20% of suitable nuclei. I do not know its significance, but I wonder whether it may not have been a similar body that Jacobs et al.[3] reported as present in nuclei of a case of XO chromosome anomaly. They considered it a possible sex-chromatin body of very small size. Such a small body also appears frequently in nuclei of oral smears from male cats (unpublished observations) when the same staining technique is used. Guard [4] in using a stain considered specific for sex chromatin described such a small body in nuclei from males. Thus far there has been no question of confusion between this small body and the sex-chromatin body of females because of the definite difference in size. However, it is my impression that use of aceto-orcein rather than cresyl echt violet as a routine stain emphasises its presence.

Ranier School,
Buckley,
Washington, U.S.A. HORACE C. THULINE.

TRACHEOTOMY AND EMPHYSEMA

SIR,—The chief conclusion of the interesting paper by Dr. Harris and Dr. Houston (Nov. 25) was: "the striking feature in each of our cases was the patient's inability to cough up his thick tenacious secretions"; and one notes that three of the four necropsies showed "obstructive bronchitis and bronchiolitis".

It seems that, vitally necessary as tracheotomy may undoubtedly be in these cases, the problem of sticky suffocating secretions has not been satisfactorily solved in these three cases. It might be worth considering the possibilities of therapeutic bronchial lavage, which seems to work very well in the similar problem of intractable status asthmaticus.[5]

Institute of Clinical Research,
Middlesex Hospital Medical School,
London, W.1. BRYAN BROOM.

SIR,—I was very interested in the paper by Dr. Harris and Dr. Houston. I only wonder why they closed the tracheotomies when the emergency was over.

They say: "We feel that the fear that the patient may become dependent upon the tracheotomy is exaggerated." Surely if the patient does become dependent on his tracheotomy it is because it is beneficial. Permanent tracheotomies are done in horses for "broken wind" with excellent results in subsequent performance. The disability of a permanent tracheotomy is certainly less than that of the severest degree of emphysema.

Does it in fact give any lasting relief in this most distressing condition?

Dorchester, Dorset. C. HOLLINS.

SIR,—I should like to support the view expressed by Dr. Bradley and his colleagues (Dec. 2) in their comments on the article by Dr. Harris and Dr. Houston (Nov. 25) on the value of pCO_2 estimations in the management of "pulmonary failure" from emphysema and chronic bronchitis; but I believe that pCO_2 values must be interpreted in conjunction with the arterial pH. The pCO_2 can vary widely in "chronic" states of respiratory insufficiency, patients frequently being conscious and sometimes even rational at levels of 120–140 mm. with the arterial pH in the region of 7·3. Similar pCO_2 levels in the acute case tend to be associated with pH values of 7·2 or less, and if a single parameter is called for as an indication for tracheotomy I would suggest that it is in a pH of this order or less.

Dr. Harris and Dr. Houston seem to have made little use of nikethamide in their supportive therapy. This is surprising, because in this area we commonly find that doses of 6–10 ml. intravenously can be expected to restore consciousness in the comatose patient in a few seconds, though the effect seldom lasts longer than half an hour.

Southern General Hospital,
Glasgow. G. J. ADDIS.

MERALGIA PARÆSTHETICA TREATED BY LATERAL MARSUPIOPEXY

SIR,—In addition to the methods of treating meralgia paræsthetica described in your annotation of Nov. 18, one further operative procedure should perhaps be mentioned which I have known to be rapidly effective in an established case: namely, correct lateral suspension of a too anteriorly placed trouser pocket—particularly if containing keys.

I have often wondered about the curious frequency of this condition in males.

University College Hospital
Medical School,
London, W.C.1. E. E. POCHIN.

ADRENAL MEDULLARY SECRETION IN HYPERTHYROIDISM

SIR,—Many relationships between thyroid hormones and catecholamines are now attracting the attention of experimental and clinical investigators. Confusion has arisen from conflicting reports concerning adrenal medullary secretion in hyperthyroidism.

Diller and Kilpatrick have reported large increases in free-adrenaline excretion in conscious hyperthyroid patients,[1] while others have reported normal adrenaline excretion in induced experimental hyperthyroidism [2] and sleeping hyperthyroid subjects.[3] It is possible to reconcile these apparently contradictory findings by recalling that a clear-cut decrease in adrenaline excretion has been described in normal sleeping subjects [4] and that psychic stimuli, such as suggestive questioning and changes in affect-state, known to be pronounced in hyperthyroidism, will specifically stimulate a large secretion of adrenaline from the adrenal medulla.[5 6]

An entirely separate phenomenon in hyperthyroidism is the sensitisation of the hyperthyroid organism to catecholamines. This has been well demonstrated with the pressor response to exogenous noradrenaline.[7] It has also been demonstrated with the oxygen-consumption increase and blood-sugar decrease following the administration of exogenous adrenaline.[8 9] Sensitisation to endogenously liberated noradrenaline and adrenaline has been demonstrated in hyperthyroid patients.[3] Realisation that many of the classical findings in hyperthyroidism are a result of such sensitisation has come from the recognition of augmented cardiovascular activity and oxygen consumption in animals with induced hyperthyroidism [10] and in human subjects with induced hyperthyroidism.[11] The abolition of such

2. Sanderson, A. *ibid.* i, 1252.
3. Jacobs, P. A., Harnden, D. G., Buckton, K. E., Court Brown, W. M., King, M. J., McBride, J. A., MacGregor, T. N., MacLean, N. *ibid.* 1961, i, 1183.
4. Guard, H. R. *Amer. J. clin. Path.* 1959, **32**, 145.
5. Broom, B. *Lancet*, 1960, i, 899.

1. Diller, W. F., Kilpatrick, R. *Brit. med. J.* 1958, ii, 823.
2. Jones, R. T., Blake, W. D. *Amer. J. Physiol.* 1958, **193**, 375.
3. Harrison, T. S. *J. surg. Res.* 1961, **1**, 77.
4. von Euler, U. S. Noradrenaline; p. 286. Springfield, Ill., 1956.
5. von Frankenheuser, M. Personal communication.
6. Zuidema, G. D., Silverman, A. J., Cohen, S. I., Goodall, M. *New Engl. J. Med.* 1957, **256**, 976.
7. Schneckloth, R. E., Kurland, G. S., Freedberg, A. S. *Metabolism*, 1953, **2**, 546.
8. Rodkinna, B. S. *Problemy Endokrinologi*, 1957, **3**, 40.
9. Hörstmann, P. *Acta endocr., Kbh.* 1954, **16**, 233.
10. Brewster, W. R., Isaacs, J. P., Osgood, P. F., King, T. L. *Circulation*, 1956, **13**, 1.
11. Gaffney, T. E., Braunwald, E., Kahler, R. L. *New Engl. J. Med.* 1961, **265**, 16.

effects by adrenergic blockade has confirmed the suspicion that these cardiovascular and oxygen-consumption effects in induced hyperthyroidism are a result of catecholamine activity.[10 11] Recently, however, Gaffney et al. and Gravenstein have pointed out that thyroid hormones also influence heart-rate independently.[11 12] Further direct effects of the thyroid hormones will probably be found as they are searched for, and observations on the effect of adrenergic blockade in patients with acquired hyperthyroidism should be made.

It is to be hoped that an appreciation of some of these relationships will help define the true nature of hyperthyroidism more accurately and eventually yield a few clues to its pathogenesis.

Department of Surgery,
Yale University School of Medicine,
New Haven, Connecticut TIMOTHY S. HARRISON.

CHEMICAL TESTS FOR PHÆOCHROMOCYTOMA

SIR,—The importance of estimating urinary catecholamines or their metabolites for the diagnosis of phæochromocytoma is now well established. The relatively simple method for free catecholamines in urine introduced by Hingerty [13] has made it possible for large numbers of urines from hypertensive patients to be examined routinely. We have heard it said that this method is unreliable and gives false positive results; the inference has been that these are false positives in the chemical sense, though several authors have found increased urinary catecholamines in the absence of a phæochromocytoma with bioassay and quantitative chemical techniques.[14–19] We should like to present evidence which indicates that positive results with Hingerty's method, in patients who are not taking drugs, probably do indicate increased secretion of catecholamines, though not necessarily the presence of a phæochromocytoma.

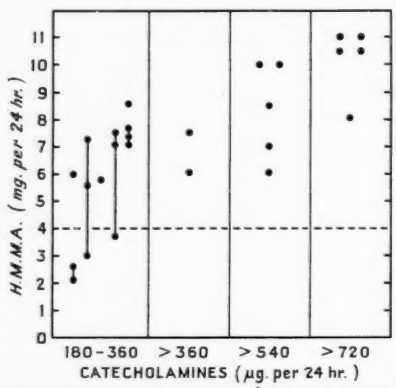

Fig. 1—H.M.M.A. excretion in hypertensive patients with increased urine catecholamines, excluding proven phæochromocytomas. All catecholamines >360 are from same case. All values of 360 or less are from other cases, those from same case being joined by lines. The horizontal line represents upper limit of normal H.M.M.A. excretion by method used.

We have examined several hundred urines from 130 hypertensive patients, 5 of whom were shown to have a phæochromocytoma. In the majority of the other patients the results were repeatedly normal, but in 12 in whom a phæochromocytoma was finally considered unlikely a high result was obtained on at least one occasion. In 11 of these, values were increased up to 360 μg. per 24 hours and higher values of up to 720 were obtained in the other. Although laparotomy was not performed in all these cases, their number makes it unlikely that they all have a phæochromocytoma. At first it was thought that these were false positive results due to other fluorescent substances, but subsequent estimation of the catecholamine metabolite 4-hydroxy-3-methoxymandelic acid (H.M.M.A.) in some of these urines showed that this measure of catecholamine secretion was also increased (fig. 1). In the cases in which this was done H.M.M.A. was increased on some occasions in all except 1; the two urines from this case had been acidified and stored at −15°C for seven months but were infected and had become strongly alkaline. H.M.M.A. was also estimated semiquantitatively by the same method (modified from Robinson et al.[20]) in 250 other urines from hypertensives with normal catecholamines, and in only 6 were slightly raised values of up to 8 mg. per 24 hours obtained. Others have also found increased excretion of H.M.M.A. in the absence of a phæochromocytoma,[6] values as high as 10 and 15 mg. per 24 hours being obtained in 2 such cases by Bollman et al.[6]

The reason for increased secretion of catecholamines in such cases is not known, though a fourfold to sixfold increase may

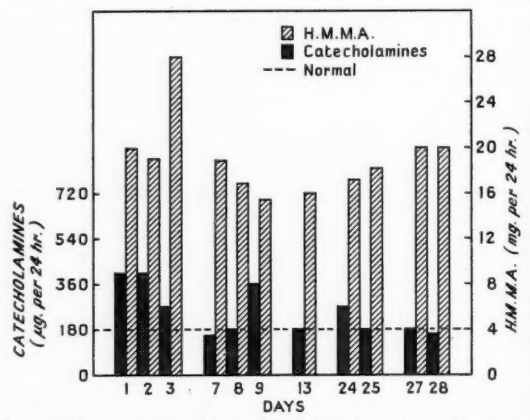

Fig. 2—Urine catecholamines and H.M.M.A. in patient with phæochromocytoma. A male aged 35 was found to have sustained blood-pressure of 180/120. He would admit to no symptoms suggestive of a phæochromocytoma; one weighing 90 g. was found at laparotomy. Reserpine was given during period of last 4 results.

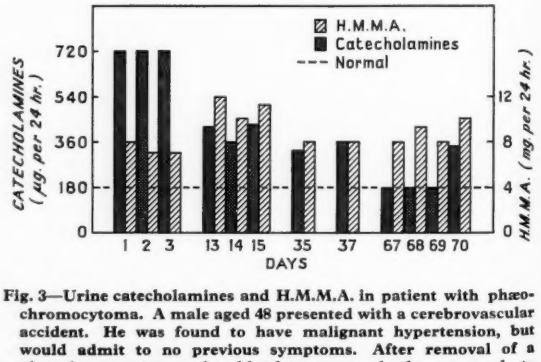

Fig. 3—Urine catecholamines and H.M.M.A. in patient with phæochromocytoma. A male aged 48 presented with a cerebrovascular accident. He was found to have malignant hypertension, but would admit to no previous symptoms. After removal of a phæochromocytoma the blood-pressure slowly returned to normal. Reserpine and phentolamine were given during the last 4 specimens.

12. Gravenstein, J. S. *Pharmacologist*, 1960, **2**, 65.
13. Hingerty, D. *Lancet*, 1957, i, 766.
14. von Euler, U. S., Hellner, S., Purkhold, A. *Scand. J. clin. Lab. Invest.* 1954, **6**, 54.
15. Ewer, R. W., Arkins, J. A., Hefferman, B. T., Lennon, E. J. *J. clin. Endocr.* 1959, **19**, 1037.
16. Comens, P., Perry, H. M., Schroeder, H. A. *J. Lab. clin. Med.* 1960, **55**, 748.
17. Sunderman, Jr., W. F., Cleveland, P. D., Law, N. C., Sunderman, W. F. *Amer. J. clin. Path.* 1960, **34**, 293.
18. Bollman, J. L., Flock, E. V., Roth, G. M., Kvale, W. F. *J. Lab. clin. Med.* 1960, **56**, 506.
19. Kraupp, O., Stormann, H., Bernheimer, H., Oberaus, H. *Klin. Wschr.* 1959, **37**, 76.
20. Robinson, R., Ratcliffe, J., Smith, P. *J. clin. Path.* 1959, **12**, 541.

occur in various forms of physical and emotional stress.[21] In some of the patients mentioned above, paroxysmal left ventricular failure undoubtedly gave rise to considerable anxiety, but this was not apparent in all cases.

The interpretation of slightly increased excretion of catecholamines or H.M.M.A. is difficult, since there may be very little increase in some patients with phæochromocytoma [22 23] (figs. 2 and 3). In some cases H.M.M.A. has been greatly increased when catecholamines were normal [19 24] or only slightly raised (fig. 2), but the converse is also true. In the case illustrated in fig. 3, although H.M.M.A. was consistently increased, the increase was relatively less than that of catecholamines in the first three urines, and the latter were more informative than H.M.M.A. in this case. Gitlow et al.[23] had 3 cases with catecholamines of 1170, 630, and 1050 μg. per 24 hours with H.M.M.A.s of 5·6, 5·6, and 6·0 mg. per 24 hours respectively. Findings have been similar in noradrenaline-secreting neuroblastoma.[25]

The number of phæochromocytomas reported in which both H.M.M.A. and catecholamines were estimated is increasing, and it is apparent that most of these tumours will be diagnosed by estimating either catecholamines or H.M.M.A., neither test having any obvious diagnostic advantage at present. In a few cases, it is clearly necessary to estimate both, though few laboratories could do this routinely in hypertensives. Hingerty's method is the simplest and, despite its limitations, Bollman et al.[18] found it as reliable in the diagnosis of phæochromocytoma as quantitative spectrofluorimetric estimation of catecholamines. The day-to-day variations in excretion of catecholamines in patients with sustained hypertension due to a phæochromocytoma is illustrated in figs. 2 and 3, and by another case in which catecholamines of 200, 1200, and 400 μg. were obtained in three consecutive 24-hour urines. We believe that Hingerty's method is adequate for screening hypertensives provided more than one urine is examined as a routine, estimation of H.M.M.A. or other metabolites being performed in cases where results are difficult to interpret. In 17 normal urines and the majority of urines from hypertensive patients, we have obtained values of less than 90 μg. per 24 hours, and regard values approaching the 180 μg. standard as an indication for further estimations of both catecholamines and H.M.M.A.

Our thanks are due to our clinical colleagues for access to case-records and for permission to include details of their cases.

Department of Pathology,
The Royal Hospital,
Wolverhampton.

J. KELLEHER
G. WALTERS.

NIGHT-CALL SERVICES

SIR,—I should like to redress the balance somewhat by offering a short letter in favour of the night-call services. While agreeing with almost every item listed by "Diplomate" in last week's *Lancet* (indeed I feel certain we both work for the same firm), I would nevertheless like to mention a few critical points.

The work is varied, interesting, and stimulating and forms an ideal, and one hopes useful, recreation for a research-worker. In about 1700 calls I have been given a wrong address about half a dozen times, and on all but one of these occasions the address was wrongly transmitted from a doctor's surgery to the headquarters of the organisation. I have never yet been "too late" for any reason. Information given by the headquarters is unavoidably vague; such information as there is seldom bears any relation to the situation found on arrival. Naturally, morphine and pethidine being schedule-IV poisons are not issued except under signature.

I have certainly had to go to extraordinary lengths to get anything approaching regular payment; but the threat of public and legal proceedings produces a gratifyingly quick response.

I think that, provided one enjoys one's medicine and is as thick-skinned as may be necessary, one can have both an interesting and a profitable part-time job with a night-call service. I manage to put in 7 sessions a week and also do a full-time research job, receiving (net) £11 a week, plus full use and resale value of the car, and still have 4 free evenings a week.

A REASONABLY CONTENT POSTGRADUATE.

PARKING

SIR,—Your peripatetic correspondent (Nov. 25) seems to imply that if, "because the specialist can't arrive in time", the number of patients dying is small, all is well, But should doctors not mind if even one patient's life is put in jeopardy?

The other day, when called to an emergency, I was distressed because collecting my car added 10–15 minutes to the journey. I asked the appropriate—and no doubt harassed beyond bearing—department of the B.M.A. why general practitioners were allowed to keep their cars close at hand while consultants were not.

The answer was that this distinction had been made "at Ministry level", because it was often represented to a general practitioner that a case was urgent when in fact it was not, whereas (my italics) *consultants are usually called only to genuine emergencies*. Have we gone through the looking-glass?

London, W.C.1. PORTIA HOLMAN.

CARDIAC DEFIBRILLATION

SIR,—An intriguing method of cardiac defibrillation, described by Negovsky,[1] uses a single electrical impulse furnished by a high-capacity condenser discharge, which he states is effective even through the closed chest. Full description and illustrations of the method in the monograph by Gurvich [2] indicates that the high voltage he uses (3000–6000) requires extraordinary insulation and precautions against current leakage which render it too unwieldy for emergency use.

Recently developed electronic photoflash equipment uses the same principle of a condenser discharge, generally with a voltage of 450 or 600 volts, and very light battery-operated models are available whose energy output of 30 to 150 watt-seconds is of the same order of size as alternating-current defibrillators deliver. Has anyone tried these for cardiac defibrillation? With some units it might be necessary to add an inductance to prolong the discharge to $^1/_{100}$ second, which seems to be about the optimum time for myocardial stimulation.

Livernois Clinic
Detroit,
Michigan.

SAM. I. LERMAN.

MAGNESIUM SULPHATE IN THE TREATMENT OF ANGINA

SIR,—From time to time letters have appeared in your journal inquiring about the efficiency of intramuscular magnesium sulphate in the treatment of coronary arterial disease,[3] without any authoritative reply being forthcoming.

Selye has demonstrated experimentally that magnesium has a protective action against cardiac infarcts in rats [4] and remarkable results have been reported in a series of 100 patients treated by Parsons in Tasmania. [5 6]

For the past nine months I have given intramuscular injections of 1 ml. of 50% magnesium sulphate solution (B.D.H.) fortnightly without any side-effects to patients with severe angina or a history of coronary thrombosis, and in 1 case in conjunction with long-term anticoagulant therapy.

21. Elmadjian, F. *in* Symposium on Catecholamines; p. 409. Baltimore, 1959.
22. Litchfield, J. W., Peart, W. S. *Lancet*, 1956, ii, 1283.
23. von Euler, U. S., Ström, G. *Circulation*, 1957, **15**, 5.
24. Gitlow, E. S., Mendlowitz, M., Khassis, S., Cohen, G., Sha, J. *J. clin. Invest.* 1960, **39**, 221.
25. Voorhess, M. L., Gardner, L. I. *J. clin. Endocrin.* **21**, 321.

1. Negovsky, V. A. *Circulation*, 1961, **23**, 452.
2. Gurvich, N. L. Fibrillation and Defibrillation of the Heart. Moscow, 1957.
3. Craddock, A. L. *Lancet*, 1960, ii, 1348.
4. Selye, H. *Brit. med. J.* 1958, i, 599.
5. Parsons, R. S. *Med. Proc.* 1959, **5**, 487.
6. *Brit. med. J.* 1960, i, 292.

The period of treatment has been too short to allow any conclusion to be drawn about the efficacy of the treatment in preventing coronary thrombosis, but I have been impressed by its effect on the 5 patients with really severe angina.

Before treatment in each case there had been severe attacks of pain lasting for several hours, accompanied by sweating and nausea, and often needing morphine to relieve them. These have now either ceased completely or been greatly reduced in severity and duration.

None of the patients reported any reduction in short-lived anginal attacks as one would have expected if suggestion had played a part.

Considering the effort expended on trials of mono-amine-oxidase inhibitors in angina it is very hard to understand why more attention is not being given to the investigation of what might well be a far more important and rewarding form of treatment. It is to be hoped that if hospital workers do not institute a large trial, the College of General Practitioners will do so in the very near future.

Belfast. S. E. BROWNE.

PRESENTATION TO SIR JOHN BOYD

Prof. G. J. Cunningham writes:

"A number of friends are planning to present Sir John Boyd ('J. S. K.') with his portrait. Would anyone who would like to be associated with this gift kindly communicate with me at the Royal College of Surgeons, London, W.C.2."

WORK FOR MARRIED WOMEN DOCTORS

SIR,—It is well known that there is, throughout the country, a shortage of doctors to do locums, especially in general practice. It is also probable that there are a number of married women doctors who, because of their domestic commitments, cannot work either full time or far from their homes, but who would be able and willing to work part time, or even full time for short periods, within their own areas.

The Medical Women's Federation is anxious to contact such women, not only in an attempt to assist general practitioners with much-needed locum help, but also because we believe that there are many medical women who would like to resume active work after having had to give up practice for a time, and who do not know how to do so.

We should be grateful if any woman doctor, whether a member of the Medical Women's Federation or not, in this situation, who is looking for locum or other work and who cannot, as yet, find employment, would write to the secretary of the Medical Women's Federation, Tavistock House North, Tavistock Square, London, W.C.1.

JOYCE COCKRAM
President

ANNE BOLTON
Honorary Secretary,
Medical Women's Federation.

Public Health

Is Notification Useful?

THE annual report of the medical officer of health for Ilford usually contains something of more than local interest; and in his report for last year Dr. I. Gordon draws attention to some oddities in the notification of food-poisoning and dysentery. Eighty-seven doctors reported 382 infections, but 195 of these were reported by two doctors. If all the doctors in the borough had notified at the same rate, the annual total would have been near 8000 cases. The figures may, of course, be true as they stand—a localised outbreak of food-poisoning arising from one small shop might explain the anomaly—but Dr. Gordon thinks that better notification would in fact give him a truer picture of the incidence of diarrhœal disease. On the other hand, investigation of these infections would call for a considerable increase in his staff without any promise that their number would be diminished.

Notification was introduced in 1899 and the list of notifiable diseases has been extended many times since then. The original catalogue was made up of diseases which called for immediate practical measures by the health department—smallpox, cholera, and enteric fever. Most of the diseases could be diagnosed at the bedside with fair certainty by the standards of the day. Many of the patients and some of their contacts would be removed to the isolation hospital where diagnoses could be checked or corrected. Today it is still unlikely that many cases of enteric fever or diphtheria escape notification, but of all the original list only scarlatina remains a relatively common disease. Later additions to the list were plague (1900), tuberculosis (1912), ophthalmia neonatorum (1914), malaria, dysentery, primary and influenzal pneumonias (1919), puerperal pyrexia (1926), measles and whooping-cough (1940), and some infectious diseases of the nervous system (1949). Other diseases such as food poisoning and anthrax have been notifiable under other Acts.

It is interesting to look at the reasons for these additions and the results. Plague was a real threat in 1900: it might be so again, though this is unlikely. The notification of tuberculosis has justified itself over and over again. Ophthalmia neonatorum and puerperal pyrexia—the only disease with a legal definition—were made notifiable in response to a general recognition that these were preventable, and the results have fully justified this action. Malaria and dysentery were added at a time when many convalescent soldiers were returning from the Balkans. Whooping-cough and measles were, we believe, made notifiable as a part of a general plan to reinforce preventive medicine in face of the stresses of war.

The practice of medicine is always changing, and the diagnosis of many of the later additions to the list calls for the aid of the laboratory—which by itself makes nonsense of notification as originally designed. We know that poliomyelitis diagnosed at the bedside will include diseases caused by other viruses: yet if we limit the diagnosis to patients from whom poliovirus has been isolated we shall understate the number considerably. Acute diarrhœa may be due to so many agents—bacterial, protozoal, viral, chemical, and dietary—that notification on clinical appearances does not get the M.O.H. very far. A wise old family doctor once remarked that three cases in a household are scarlatina but two are just streptococcal sore throat. Few understand the distinction. Another change is that, when notified of sporadic cases of most of the diseases on the list, the M.O.H. can do precious little to prevent further spread: modern treatment ensures that by the time the notification arrives the patient is no longer infectious. Epidemics are another matter, and we have every sympathy with the M.O.H. who, without a single notification on the table, knows that half the children in the town have Sonne dysentery.

Dundreary whiskers, scarlet uniforms, therapeutic vaccines—it is easy to find defenders of all these relics of

an age long past; and, if we suggest that notification of infectious disease deserves reconsideration, pens will fly from a thousand pockets to tell us that we err. Yet it would be interesting to know, for each disease on the list, what proportion of cases are notified and how the practice varies from place to place. Smallpox (when diagnosed), enteric fever, diphtheria, tuberculosis, puerperal pyrexia, anthrax, and probably paralytic poliomyelitis are likely to be notified reasonably accurately. If the object of notification is to help the M.O.H. in the control of infectious disease, the above list is long enough; but there are other diseases not yet notifiable about which he ought to know. As a source of medical statistics notifications mean very little: for example, in the borough of Ilford no cases of whooping-cough, measles, or scarlatina were notified in 1960. (Dr. Gordon's report makes no mention of the use of legal sanctions to enforce the Public Health Act. Is this ever done nowadays?)

In some places the medical officer of health has other less official sources of information. Some bacteriological laboratories send copies to the health department of all reports likely to be of interest. Objection has been raised to this as a breach of professional secrecy, but experience shows that most family doctors are glad to make the information available for the public good. (What they do dislike is the sequel when, quite unannounced, a raw young health inspector comes to demand fæcal specimens from a modest maiden lady.) Such information from the laboratory tells the M.O.H. nothing, of course, about measles, and little about whooping-cough; but what he learns about the diarrhœal diseases and streptococcal infections is more accurate than that derived from clinical diagnosis. In addition, he will get news of brucellosis and leptospiral infections, and a whole host of viral diseases of greater and less importance.

As a source of statistical material these laboratory reports are unreliable: just as some doctors seldom or never notify, some never send specimens to the laboratory. If anyone wants to know the incidence of non-fatal disease in his community he must turn to such sources as weekly payments of sickness benefits by the Ministry of National Insurance, or the attendance registers at the schools. Or, if he seeks greater accuracy, he must adopt the methods used so brilliantly by Prof. A. L. Cochrane in the Rhondda Fach—and that really will mean an increase in the size of his department.

Infectious Diseases in England and Wales

Diseases	Week ended November			
	4	11	18	25*
Diphtheria	..	2	..	3
Dysentery	386	345	418	510
Encephalitis:				
Infectious	3	3	3	1
Postinfectious	1	..	..	..
Food-poisoning	329	116	98	125
Measles, excluding rubella	1145	994	938	1082
Meningococcal infection	17	14	14	27
Ophthalmia neonatorum	17	19	16	17
Paratyphoid fever	6	12	7	4
Pneumonia, primary or influenzal	161	168	179	222
Poliomyelitis:				
Paralytic	50	29	21	29
Non-paralytic	20	17	6	7
Puerperal pyrexia	153	146	143	196
Scarlet fever	378	374	414	493
Smallpox	..	..	..	..
Tuberculosis:				
Respiratory	324	332	340	376
Meninges and C.N.S.	10	3	2	3
Other	52	48	59	40
Typhoid fever	6	7	15	..
Whooping-cough	207	194	200	193

* Not including late returns.

Parliament

Too Few Doctors

IT is painfully easy to overlook the obvious when it comes on one gradually, as Lord TAYLOR pointed out on Nov. 29, when calling attention to the grave shortage of doctors. Until he started to investigate the situation a few months ago he had no idea how serious it was. He found that though the population had increased between 1939 and 1958 by 10% the number of medical students was up by only 7%. Furthermore, as it took seven years to make a doctor, there was nothing that we could do now to increase the number of doctors who would come forward in the next seven years. How had this been allowed to happen? It had started in 1953, when hospitals in the North and in the Midlands began to have difficulty in filling their junior posts. Since then it had grown steadily worse. Yet in 1958 the Willink report proposed a cut of 10% in the number of medical students. Fortunately this had never been fully implemented by the medical schools. Nevertheless, between 1956 and 1960 the number of medical students starting their courses had dropped by 200 a year. Lord Taylor thought that the Willink Committee, misled by official figures, had underestimated the speed of growth of population. They had also underestimated the number of doctors who would be needed for research, industry, teaching, and the Services. They had underestimated the needs of the population for general practitioners, and they had overestimated the number of general practitioners who would remain at work once the N.H.S. retirement pension became payable.

Many hospitals already had difficulty in filling posts. Lord Taylor quoted figures for the Sheffield region, where of 705 advertised registrar posts only 188 were filled, and only 50 of these by "homegrown" doctors. In the teaching hospitals the position was better, but recently two of them had had difficulty in filling registrar posts in general medicine. The whole of our hospital service would have collapsed had it not been for the enormous influx of junior doctors from India and Pakistan. There were now working in our hospitals 3000–4000 doctors trained in India and Pakistan. These doctors and others from medical schools of Egypt, Israel and Africa, Malta and Portugal, Turkey and China, Greece and Ceylon were usually less experienced than our own graduates at the same stage, for their teaching was rather different. They were coming here to learn, and they were going to the worst places to do it, where there was less supervision. Most of them did a very good job, but he feared that, through no fault of theirs, there was a general lowering of standards of hospital care, especially in casualty work. We should be proud that they wanted to come to us and learn. But we were not treating them fairly.

In general practice, too, the shortage was starting to show itself here. Three years ago, there were 30–50 applicants for a good general practice in the South of England. Today there were often only 6–8. In a less attractive area, where there used to be 6–8, there were now 1 or 2, or even none. For consultants it was the same story—applications halved. In the less popular specialties—psychiatry, radiology, ear, nose and throat surgery, anæsthetics, and sometimes pathology—there were few applicants, so that posts were being re-advertised.

The shortage, he feared, would get worse as the population grew in the next seven years, with no increase in the number of doctors coming forward. Moreover, there would be a peak of retirements among specialists in the next five years, for many had entered the specialties and started to train at the end of the 1914–18 war.

The Ministry was trying two palliatives. First, it was offering an extra £100 a year to supplement the pay of posts in "black area" hospitals. All this could do at the best was to alter the distribution; it would not increase by one the number of doctors. Secondly, it looked to the general practitioners to help in the hospitals. But general practice, outside the South of England, was already strained to breaking point.

We could not much increase the intake to our existing medical schools without jeopardising standards of teaching. Instead we must have 3, and preferably 6, new medical schools without delay. Lord Taylor proposed that as a crash programme we should open first-year medical courses next October at, say, the following places: Southampton, the Central Middlesex Hospital in North London, and Nottingham. This would give time to build up the teaching for second and subsequent years. All that was needed was hutted laboratories and the first-year teachers; and, given the proper sense of urgency, both could be produced in time. In the great modern conurbations in Birmingham and Manchester, there was room for second medical schools, taking the local university degrees. We must also have at the Ministry of Health a proper statistical department, to review continuously and intelligently the state of the health service. He also proposed establishing four short-course training centres, to which doctors from underdeveloped countries should go for 6–8 weeks to be taught something about the work they were going to do, especially emergency casualty techniques, the service in which they were going to work, the patients they were going to care for, and the role they would have to play, especially in their relations with other doctors inside and outside the hospital. The British Council could help them to brush up their English. These centres could also help to place them properly according to their capacity and our needs.

Lord EVANS agreed that we are facing a " fantastic shortage " of doctors. A quarter of all house-officers came from overseas and half the emergency surgery was carried out by them. He hoped that their Lordships would bear this problem in mind when they came to consider the Immigration Bill.

The situation seemed extraordinary, for at the same time it was impossible for a student to gain entry into any medical school until 1963. As far as he knew no plans were ready for any major increases in medical students. He thought, however, that most teaching hospitals could easily, and without any disadvantage, take an extra 10% of students. The real difficulty was the bottleneck in the preclinical subjects, and he was not as confident as Lord Taylor of getting plenty of teachers in these subjects. Nor would it be easy to find the necessary accommodation. Some of these difficulties could be reviewed by peripatetic visitations by the Ministry and the University Grants Committee. He believed that doctors should be dissuaded from emigrating and that better postgraduate facilities for overseas doctors should be instituted as soon as possible. A committee should be set up to hold a continuous review of the situation, and he emphasised the word " continuous ".

Baroness SUMMERSKILL offered two suggestions to stimulate general practice—the introduction of some form of financed inducement in unattractive areas and of a system whereby the older doctor could transfer to an easier practice where he could continue to work after passing the age of 65. She found it curious that the debate should synchronise with the widespread discussions on the Immigration Bill. Despite the prejudice which was alleged to exist, a man was quite prepared to accept for himself and his wife, without protest, the intimate doctor-patient relationship with a coloured doctor. There was nothing but praise and gratitude for the services of our coloured immigrant doctors and auxiliary workers. It would seem that when a person was sick he became more rational and less prejudiced.

Lord COHEN OF BIRKENHEAD, who was a member of the Willink Committee, recalled that it was appointed at a time when there was general concern in the profession that there was a surplus of doctors. On publication the report had been well received by all the papers, medical and national. He readily admitted that events had falsified some of the committee's assessments, but in the report they had been described as necessarily speculative. But whether or no the Willink Committee was right, was not significant. The crux of the matter was: Are there sufficient doctors? In his view there were not. We needed more doctors to correct the false assumptions of the Willink report on population trends and on the age of retirement of doctors; to reduce the average of patients on the doctor's list, in urban areas to 2500 and in rural areas to 2000; and to still further expand our consultant and specialist hospital services. He agreed with Lord Taylor that we should increase our intake of students by about 250 a year. But like Lord Evans he thought that the preclinical years were the difficulty. It might become necessary to establish a new medical school, but he deprecated Lord Taylor's suggestion that it should be associated with the Central Middlesex Hospital because all medical schools should be an integral part of a university. Since doctors tended to settle in practice near their medical school, might it not be well to attach the new school to one of the universities in the north?

He emphasised that we must make the best use of our present resources, and that might well depend on reorganisation of hospital staffing. The supply of doctors was a dynamic, not a static, problem. There were too many imponderables for a rigid solution. The situation might change overnight. If within the next twenty-four hours there was discovered a drug which would cure cancer, then 150 consultant radiotherapists would be out of work, and the work of the surgeons would be considerably reduced. On the other hand, new specialties might arise, as they had done in the past. There might well soon be a change in the type of practice, with greater emphasis on domiciliary practice as contrasted with hospital practice. And, of course, we might in the future make greater use of the professions supplementary to medicine and spare the doctor. What was needed was a regular annual review of graduates, medical-school intakes, and the like, undertaken in detail by the Health Departments, so that immediate decisions could be taken.

Lord STONHAM wondered how we were going to provide an efficient and safe hospital service while exporting British doctors at the rate of about 600 a year and importing 700–800 doctors, mainly from underdeveloped countries.

Lord NEWTON, replying for the Government, said that the review of the data and conclusions of the Willink report had now been completed, and the Government were satisfied that the prospective demand for medical services would justify a rise in the university intake of preclinical students from Great Britain of 10% above the level recommended by the committee. The Chief Secretary to the Treasury had asked the University Grants Committee to consider with the universities the implications of the Government's conclusion. This being so, it would be premature for him to say more about numbers and capacity of medical schools than that he found it hard to imagine that the Government would be able to approve the very large increase for which Lord Taylor called.

Turning to the question of doctors from overseas, he said that it was true that over a third of the posts in the middle and lower grades of the hospital service were, in March, 1960, occupied by doctors born outside this country. Lord Taylor's suggestion that there should be special training and indoctrination centres for these doctors ignored the fact that regional hospital boards, hospital management committees, and boards of governors had complete discretion in their appointments. To insert a training school between one group of fully registered medical practitioners and their potential employers would be a slur not only upon the qualifications and training that these people obtained in their home countries, but also upon their prospective employers, who were expected to exercise informed discretion over the persons they appointed, and to ensure that after appointment any necessary supervision was given.

The Government were fully aware that the number of doctors must be watched in the interest of the health service. They considered, however, that it would be rash to provide at infrequent intervals, as in the past, categorical estimates of exactly what the disposition of and need for doctors would be at distant future dates. Instead they proposed to keep evidence of demand and supply under continuing review, and to try to maintain a flexibility of approach to the problem which had not hitherto been achieved.

Profits of Drug Firms

One of the points to which Mr. HAROLD WILSON drew attention on Nov. 30, when, as chairman of the Select Committee of Public Accounts, he opened a debate on the committee's reports, was the profit percentages of British

subsidiaries of American pharmaceutical manufacturers. Last year the committee had been hampered by lack of information; this year the Ministry of Health had provided an accountant's report. Accepting the companies' own statement of the cost of research undertaken in the United States, the accountants found that the percentage of profit ranged from 18·4 to 44·8 with a weighted average of 33·67, which was high in relation to figures for British and Swiss companies. The Ministry had accepted that the figures were too high and had entered into negotiations with the companies. Mr. Wilson believed that during the past year there had been a great improvement in the Ministry's approach to this problem, but he did not feel satisfied with what had so far been achieved. For instance, the figures given for the American element in the cost hardly squared with the impression gained from a study of the evidence presented to the Kefauver Committee which had been making a parallel inquiry in the United States.

Advertising costs were also an element in fixing prices, and the Select Committee had asked for further figures. They had been told that mail advertising and free samples amounted to 4·31% of total net sales of £50 million, but this did not include sales promotion by door-to-door representatives which was known to be considerable. He was disturbed to see from the Treasury minute on the committee's report that the Ministry had still not been able to obtain from the industry the information for which it had asked.

Sir EDWARD BOYLE, financial secretary to the Treasury, in his reply said that the voluntary price regulation scheme was being worked out with the pharmaceutical industry, and that the Treasury felt that it would be difficult to safeguard Exchequer interests by concentrating too much on the concept of what one might call a reasonable profit on capital. He believed that the best way to approach these firms was by direct negotiations about prices of widely used drugs. Already the Ministry of Health had investigated the figures of the cost and profits of certain companies, so far as it could in the light of the information supplied. It had put some specific questions to the drug companies about the cost of advertising. He agreed that the industry must be frank with Government departments, but he thought that it might be genuinely difficult for the industry to say just what its costs were in all cases. But the Treasury and the Ministry were certainly not going to drop the matter.

Professions Supplementary to Medicine

A group of M.P.s from all three parties have signed the following motion:

That this House is concerned at the grave shortage of qualified dieticians, occupational therapists, orthoptists, physiotherapists, radiographers, and remedial gymnasts in the National Health Service and its effects on the national economy: and calls upon the Minister of Health to appoint an independent committee to review and report upon the present arrangements for recruitment, retention, grading, and remuneration of members of these professions in the National Health Service, and to make any recommendations considered necessary.

Sir Hugh Linstead is the main signatory, and his supporters include Dr. Barnett Stross and Dr. Donald Johnson. Dr. Johnson wishes to include audiological technicians in the motion.

QUESTION TIME

Willink Report

Mrs. E. HILL asked the Minister of Health when he expected the review of the data and calculations underlying the Willink report to be completed.—Mr. ENOCH POWELL replied: This review has now been carried out. The Secretary of State for Scotland and I are satisfied that the prospective demand for medical services would justify a rise in the university intake of preclinical students to 10% above the level recommended by the Willink Committee. The Chief Secretary to the Treasury has asked the University Grants Committee to consider with the universities the implications of this conclusion.

Prices of Drugs

Mr. J. J. THORPE asked the Minister on what date he expected it would be possible to procure the antibiotics tetracycline, chlortetracycline, oxytetracycline, and chloramphenicol for National Health Service prescriptions at the same price as was now being paid by his department when purchasing these drugs for the hospital service.—Mr. POWELL replied: I would hope that the terms of supply to the general pharmaceutical services will be influenced by the price to the hospital service; but there are a number of differences which make direct comparison impossible.

Mr. KENNETH ROBINSON: If the Minister's hopes are not realised, would it not be possible for him to vary his contract with the chemists so as to require them to purchase these four drugs through him for the purpose of dispensing National Health Service prescriptions? Mr. POWELL: I would have to consider whether I have statutory powers for that, but I shall certainly watch continuously and closely the effect of the current procedure.

Cosmetic Operations

Mr. L. ABSE asked the Minister whether he would introduce legislation to prevent unregistered medical practitioners carrying on cosmetic operations for such purposes as remodelling busts, straightening and shortening noses, removal of pouches under the eyes, and correcting obtruding ears, in view of the disfigurement and danger to health which may result from this class of operation.—Mr. POWELL: No, Sir. Mr. ABSE: Is the Minister aware that there are in existence beauty bureaux sending out advertisements publicly inviting people to have all these operations performed upon them, that the operations are performed by quacks and people who have never had any medical qualifications whatever, and there is ample evidence that they cause serious harm? Does the Minister not consider it a very unsatisfactory position that, whereas a person cannot obtain spectacles except from a registered optician, or dental treatment except from a registered dentist, it is possible for anyone with impunity to wield a surgeon's scalpel with very serious results?

Mr. POWELL: I have no evidence of harmful effects from the kind of treatment mentioned, but if he will let me have the evidence to which he has referred I shall look into it.

Psychotic and Maladjusted Children

Mr. KENNETH ROBINSON asked the Minister of Health if he would enumerate the special units in each hospital region for the care and treatment of psychotic and severely maladjusted children, other than subnormal and severely subnormal children; and what was the number of staffed beds in each.—Mr. POWELL replied: The information is as follows:

Region	Unit	Staffed beds
Newcastle	St. Luke's Hospital, Middlesbrough	12
Sheffield	Mapperley Hospital, Nottingham	22
North West Metropolitan	High Wick, Tyttenhanger	18
North East Metropolitan	Whipps Cross Hospital	12
South East Metropolitan	Maudsley Hospital	24
South West Metropolitan	Belmont Hospital	12
Oxford	Park Hospital for Children	30
	West Stowell House, Oare	36
	Smith Hospital, Henley	46
South Western	Merrifield. Tone Vale Hospital	36
Wales	Gwynfa	3
Birmingham	South Warwickshire Hospital	6
Manchester	Booth Hall Hospital	9
Wessex	St. James's Hospital	30

Medical Research and Children

Mr. ROBERT MATHEW asked the Minister how many controlled clinical experiments in the interests of medical research had been carried out on mentally subnormal children in the last 12 months.—Mr. POWELL replied: A measles vaccine was given to a group of patients at the Fountain Hospital and Queen Mary's Hospital, Carshalton, before an anticipated outbreak of measles. There were no ill effects apart from the reactions of modified measles. Otherwise, I am not aware of any controlled clinical experiments apart from those connected with research into subnormality. Mr. MATHEW: Will the Minister not agree that if these experiments are to be carried out at all, and in a number of cases there have been very undesirable side-effects such as high fever, preferably they should be carried out on volunteers rather than on mentally defective children? Mr. POWELL: The parents had been asked and gave consent in writing. Subnormal children are particularly liable to measles and, therefore, this test was particularly relevant to subnormal children. Captain WALTER ELLIOT: Is the Minister aware that I have discussed this matter with the senior medical officer of this hospital and he has assured me that there were no bad side-effects and the only thing suffered was a slight rise in temperature and a very slight measles rash? Mr. POWELL: That coincides with my information.

Obituary

HOWARD HILTON STEWART

M.D. Belf., F.R.C.P.

Dr. H. Hilton Stewart, senior physician to Claremont Street Hospital for Nervous Diseases and consulting neurologist to the Royal Victoria, Belfast City, and Musgrave Park Hospitals, died on Nov. 25.

The elder son of the late Mr. A. W. Stewart, who was for many years editor of the *Belfast Telegraph*, he was educated in Belfast at the Royal Academical Institution and the Queen's University. After qualifying in 1923 he held house-appointments at the Royal Victoria Hospital and the Ulster Hospital for Children and Women, and then spent some years of postgraduate study in London, including a term as house-physician at the Maida Vale Hospital, where his chiefs were Dr. Douglas McAlpine and Sir Russell Brain.

On his return to Belfast he took up private practice as a physician with special interests in neurology, and in 1929 he was appointed assistant physician to Claremont Street Hospital and the Ulster Hospital and medical registrar and later clinical tutor at the Royal Victoria Hospital. In 1938, he became senior physician at Claremont Street Hospital. After the start of the National Health Service he gave up his general consulting medical practice and confined himself to neurology, and he was appointed visiting consultant to the Royal Victoria and Belfast City Hospitals, where he had charge of beds and of outpatient clinics in addition to those already established at Claremont Street Hospital and the Ards Hospital. In 1959–60 he was appointed clinical lecturer and examiner in medicine at the university. He was elected F.R.C.P. in 1951.

His capacity as an administrator was shown when he became chairman of Claremont Street and Killowen Hospitals in 1948. Through the hospital committee and as a member of the Belfast Hospitals Management Committee, he succeeded over the years in developing the resources of these hospitals, so that the actual admission of patients rose from 549 in 1948–59 to 1222 ten years later, and outpatient attendances from 1712 to 14,418. Through his initiative the electroencephalographic department was started in 1947. Departments of radiology, neuro-ophthalmology, and physiotherapy were later added. Many improvements were made in the actual fabric of Claremont Street, so that from a single house in 1896 (no. 14), the hospital façade now extends over the greater part of one side of the street. In all his work for the hospital he had the support of his wife, Clara Hilton Stewart, and after her death a ward unit was named after her.

As a member of council of the Ulster Medical Society and one-time librarian, he took a special interest in the preservation of the Whitla Medical Institute, and was secretary to the trustees. He was twice president of the Ulster Neuropsychiatric Society.

R.S.A. writes:

"Hilton Stewart was a most able clinical neurologist, who read extensively and kept himself always abreast of modern work. As was natural to one trained in London before the impact of neuroradiology and electroencephalography had made themselves felt, he had an abiding respect for the great teachers of those days whose clinical wisdom (and occasional personal eccentricities) he could recall most realistically. He was at his best when giving clinical demonstrations to students, and on ward rounds with his house-physician and registrars, where his training was reflected in his wide capacity for critical appraisal of physical signs and in the time he was prepared to give to the examination of each patient. The follow-up and control of epileptic patients was of special interest to him, and he was convinced that the neurologist had an important part to play in the diagnosis and treatment of the psychoneuroses.

"Like many other busy people with a strong critical sense, he wrote little, though when pressed to he would do so, and he contributed several articles to the ninth edition of *Whitla's Dictionary of Treatment*. It was the same with public and after-dinner speaking. He never courted opportunity, but when the occasion arose he was incomparable in his ability to hold an audience, and on one memorable occasion at a staff dinner he made a speech which will long be remembered for the exceptional quality of its wit and humour. A lover of company, he had a natural gift for making friends, and one of his regular delights was Saturday afternoon excursions to Newcastle to play golf and exchange 'crack' at the Royal County Down.

"He had been in failing health for a year, but he carried on with his hospital duties and private practice to within a few weeks of his death. One of his last public acts was to preside at the Cecil Calvert lecture in the medical school, and the simple grace and dignity with which he enriched this occasion drew admiration from all present."

Appointments

ARMSTRONG, F. C., M.B. St. And., D.P.H.: senior assistant M.O. and school M.O., West Riding of Yorkshire, and deputy M.O.H., Hoyland, Nether, Penistone, Stocksbridge, and Wortley.

PEACH, F. P., M.B. Lpool, D.P.H.: deputy M.O.H. and deputy principal school M.O., Denbighshire.

ROBERTON, PAMELA A., M.B. Lpool, D.OBST.: assistant M.O., Liverpool.

SPRY, W. B., M.B. Brist., D.P.M.: consultant psychiatrist, Herefordshire hospital group.

VEREKER, RICHARD, M.D. N.U.I., D.P.M.: consultant psychiatrist, Burton-on-Trent hospital group.

Welsh Regional Hospital Board

EVANS, T. G., F.R.C.S.E.: consultant in general surgery, Glantawe hospital group.

JONES, C. H., M.D. Lpool: second consultant pathologist, Clwyd and Deeside hospital group.

THOMAS, J. H., M.R.C.P.: consultant geriatrician, Mid Glamorgan hospital group.

Notes and News

NEW PÆDIATRIC CENTRE

WHEN he founded the Institute of Child Health at Birmingham in 1945, the late Sir Leonard Parsons hoped it would someday have a site in the Children's Hospital. He wanted it to be "a headquarters of preventive pædiatrics just as the hospital is the headquarters of curative pædiatrics". A meeting of the interested parties in 1956 decided that the new building should be "a place where general practitioners, the medical officers of the local authority, regional pædiatricians, the Children's Hospital staff, and the members of the Department of Pædiatrics and Child Health should have a common meeting ground". Laboratories should give an opportunity for joint studies by doctors from these various disciplines who shared a common interest in the health of children.

Though it may later be enlarged, the building in its present form is now coming into use. The ground floor has a conference hall and library, the first floor has some offices and a room for a lecturer, and the top floor has a large laboratory and two small ones—connected by a bridge to the department of biochemistry.

£40,000 was given by the Nuffield Provincial Hospitals Trust for the building, and nearly £20,000 by the University Grants Committee for the equipment. For maintenance an annual contribution of £3750 has been made by the Birmingham city council, while the United Birmingham Hospitals are giving £1500 for 1961–62 and thereafter £2500 a year. Another £2000 will come from the faculty of medicine for the appointment of a research assistant and technician, and the regional board will contribute £500 a year for running costs. Messrs. H. J. Heinz are giving £250 a year under covenant.

Prof. Douglas Hubble, of the department of pædiatrics and child health, is director of the institute, and the research staff includes Dr. G. H. Wolff, Dr. B. D. Bower, Dr. June Lloyd, and Dr. J. H. Edwards.

Among the particular interests will be a five-year survey (in conjunction with general practitioners) of epilepsy in children. A good deal of work has already been done on "infantile spasms", and cognate researches include a study of pyridoxine-dependent convulsions and those precipitated by watching television. As part of the investigations into blood lipoproteins, diabetic children are having a long-term controlled trial of a diet rich in unsaturated fat. One of the major interests will be the genetic and chromosomal aspects of mental deficiency, and work on growth hormone and steroid assays will be continued.

INSTITUTE OF CLINICAL RESEARCH

As usual, the Middlesex Hospital Medical School and its Institute of Clinical Research produced a lively display for their annual evening of demonstrations on Nov. 28. The director of the institute, Prof. Alan Kekwick, and the many people concerned in its research programme were able to show visitors more than thirty exhibits that reflected its expanding interests at many growing-points of medicine.

Insulin increases the rate at which fat metabolises glucose to CO_2, and in the epididymal fat-pad method of serum-insulin assay, fat is allowed to act on glucose (in a concentration of 300 mg. per 100 ml.) containing 0·2 μC of radioactive glucose [1]. In the work demonstrated by Dr. A. Willcox, Dr. D. N. Phear, Dr. I. E. Evans, and Miss A. Cameron more sensitive methods of counting radioactive CO_2 had made it possible to use smaller pieces of fat so that assays could be repeated on the same animal. The sulphonylureas cause islet-cell hypertrophy and increase serum-insulin levels; and the modified fat-pad method was used to study these effects in 6 young or middle-aged patients with early diabetes being treated with 300 mg. of chlorpropamide daily. Glucose-tolerance tests and serum-insulin assays were performed before, during, and after treatment. Normal subjects showed a striking increase in serum-insulin levels one hour after taking 50 g. of glucose by mouth. In diabetics there was no rise in serum-insulin or only a very slight one. During treatment with chlorpropamide, the diabetics showed a definite increase in serum-insulin levels and an improvement in glucose-tolerance curves. Six weeks or more after stopping chlorpropamide, serum-insulin had reverted to pretreatment levels.

1. Renold, A. E., Martin, D. B., Dagenais, Y. M., Steinke, J., Nickerson, R. J., Sheps, M. C. *J. clin. Invest.* 1960, **39**, 1487.

Dr. B. A. Sellick and Dr. Bryan Broom had been investigating the hypothermic effect of CO_2 in rats. In mammals an increase in inspired CO_2 depresses body-temperature; and experiments were performed on adult male Wistar rats to determine the action of 20% CO_2 in O_2 on colonic temperature. At room-temperature (20–23°C) this mixture lowered the colonic temperature of a normal rate by 3·6°C in one hour. A rat clipped of its fur lost 5·1°C in an hour. Deep-freeze experiments (at about 0°C) compared the cooling effects of pentobarbitone ('Nembutal') anæsthesia alone with those of pentobarbitone and 20% CO_2 in O_2 combined. The greatest rate of cooling was in clipped rats breathing the CO_2 mixture; and this rate was slightly greater than that of clipped fresh cadavers. The aim of this work is to lay the basis for an improved hypothermic technique in anæsthesia.

In some elegant experiments on refractoriness and supernormality in human peripheral nerves, Dr. R. W. Gilliatt and Dr. R. G. Willison had studied responses to two supramaximal shocks given at increasing intervals. They demonstrated an absolute refractory period of about 0·6 millisec., followed by a relative refractory period, and a period of supernormal excitability up to 10–16 millisec. The conduction-rate was shown to be slower than normal during the relative refractory period. By examining the effect of ischæmia on median-nerve conduction in patients with the carpal-tunnel syndrome, Dr. Gilliatt and Dr. P. M. Fullerton had found that susceptibility to ischæmia did not seem to be related to the severity of pre-existing nerve damage, as judged by either the initial size or the initial latency of the muscle action potential in response to stimulation. Susceptibility was, however, related to the severity of spontaneous attacks of pain and paræsthesiæ in the period immediately before the test.

The perplexing matter of idiopathic hirsutism has been interesting Dr. J. D. N. Nabarro, Dr. A. E. Kellie, Miss Audrey Moxham, and Dr. L. Lazarus. The condition might be due to stimulation of hair follicles by a hormone or to an abnormality of the follicles themselves. The common association with menstrual irregularity suggested a hormonal disturbance; and if an abnormal hormone was present it probably came from the adrenal or the ovary. Dr. B. E. Kendall's pelvic pneumograms had shown enlarged ovaries in some women with hirsutism associated with Stein-Leventhal syndrome; and Dr. Kellie had demonstrated Δ^4-androstendione in fluid from Stein-Leventhal ovaries but not in incubation fluid from ovaries in other types of hirsutism. Two techniques were used to try to uncover a possible adrenal mechanism: study of basal levels of 17-hydroxycorticosteroids and 17-ketosteroids; and stimulation of the adrenal cortex by corticotrophin gel. In hirsutism, the exaggerated response of ketosteroids was understandable because the known androgenic substances were ketosteroids; but it was harder to explain why 17-hydroxycorticosteroids should be increased, since they were cortisol metabolites.

By ingenious means of dye dilution, Dr. H. L. Marriott and Dr. M. P. Spence had been estimating flow-rates in the small intestine. A double-channel plastic tube was passed into the small bowel. One channel opened near the tip of the tube and took samples; the other was 8 in. higher up and was used to introduce phenol red, which was neither absorbed nor destroyed in the intestine. It was given in aqueous solution at a steady known rate, while the patient consumed and digested a meal. Samples were withdrawn at $^1/_4$-$^1/_2$-hourly intervals and the concentration of phenol red measured. From these data, flow-rates were estimated. By including a second marker (polyethyleneglycol) in the meal it was possible to calculate how much fluid passing the end of the tube was derived from the meal and how much from the digestive juices.

Much interest was evoked by the work on infra-red thermometry by Mr. R. S. Handley, Dr. F. J. Lloyd-Williams,

and Mr. K. Lloyd-Williams. Their use of this technique in the diagnosis of lumps in the breast is described in an article which we hope to publish later this month.

WORLD STANDARDS AGREEMENT ON HYPODERMIC SYRINGES

AGREEMENT aimed at making hypodermic syringes and their needles fully interchangeable, regardless of country of origin, has been reached by a technical committee of the International Standards Organisation.

The committee agreed on dimensions and tolerances—which are intended to become standard throughout the world—for the conical fitting used to connect hypodermic needles with syringes. These standard dimensions are for fittings with a 6% taper (the British and American custom for some years), and so there will be complete interchangeability between fittings made in accordance with the proposed I.S.O. recommendation and those of the Luer type which are already specified in British and American standards. As an interim measure the committee is also to include in its recommendations standard dimensions for a 10% conical taper. The committee has agreed on some basic requirements for hypodermic syringes and needles.

University of London

The degree of M.D. has been awarded to Harold Caplan.

University of Wales

At recent examinations for the degrees of M.B., B.CH., the following were successful:

L. S. Addicott, Hezekiah Chiadikobi Amobi, P. M. Bazzard, Beryl A. Davies, P. R. C. Davies, A. G. Ellis, Olwen Harries, W. E. Hughes, J. T. Jones, P. W. Jones, Donald Knight, W. A. Morgan, M. P. W. Rowlands, P. C. A. Thomas, H. N. Williams.

Royal College of Physicians of Edinburgh

At the annual meeting of the college on Nov. 30, the following officers were elected:

President, Dr. J. D. S. Cameron; vice-president, Prof. I. G. W. Hill; members of council, Dr. J. G. M. Hamilton, Dr. T. Anderson, Dr. A. W. Wright, Dr. H. J. S. Matthew, Dr. C. W. Clayson.

Royal Society

At the anniversary meeting of this society on Nov. 30 Sir Howard Florey was re-elected president. Among the other medical fellows Sir Lindor Brown was re-elected biological secretary, and Sir Harold Himsworth was elected a member of the council.

Royal Society of Health

Dr. James Galloway, medical officer of health for Wolverhampton, has been elected chairman of the council of this society.

Industrial Injuries Advisory Council

This council has begun a new term, and of the medical members the Minister of Pensions and National Insurance has reappointed Mr. Alan Malkin, Dr. D. G. Morgan, and Dr. L. G. Norman. The new members include Dr. Alice Stewart.

Queen Mary's (Roehampton) Hospital Transfer

The transfer of the administration of this hospital from the Ministry of Health to the board of governors of Westminster Hospital took place on Dec. 1. The administration of the limb-fitting centre will remain the responsibility of the Ministry.

Sheldon Rehabilitation Centre

The management committee of Rubery and Hollymoor Mental Hospitals, Birmingham, is to name this new hospital unit after Dr. J. H. Sheldon as a tribute to his work for old people. The unit will have facilities for 156 patients.

British Medical Students' Association

The annual general meeting of this association was held at Stratford-on-Avon from Nov. 10 to 12, under the presidency of Mr. John Bootes. An address was given by Prof. A. L. d'Abreu, the honorary president. At the end of the meeting Mr. Paul Townsend of University College Hospital Medical School was invested as president for 1961–62.

British Rheumatism and Arthritis Association

This Association has opened a recuperative holiday hotel at Birchington-on-Sea for service to its members.

The house is centrally heated and each bedroom also has an electric fire. Passage rails and bath grips are provided. There is accommodation for 14 guests in single and double bedrooms, most of which are on the ground floor. Membership fee for the B.R.A. is 10s. All inquiries for the hotel should be made to the manager, Duncombe House, Sea View Road, Birchington, Kent.

On Wednesday, Dec. 13, at 5.30 P.M., at the Fountain Hospital, Tooting Grove, London, S.W.17, Dr. Karel Bobath will speak on problems of treatment of patients with cerebral palsy and mental subnormality.

A meeting of the Biochemical Society is to be held on Saturday, Dec. 16, at 10.30 A.M., at the Postgraduate Medical School of London, Ducane Road, W.12.

Dr. W. S. C. Copeman will deliver the Woodward lecture at Yale University on Jan. 30.

The registrar of the Council for Professions Supplementary to Medicine is Mr. J. S. Tapsfield. The address of the Council is St. Luke's Hospital, Sydney Street, London, S.W.3.

Hospital Building Note no. 14 deals with the design of training schools for nurses. It contains a loose-leaf sheet, issued as an addendum to Hospital Building Note no. 2, which gives details about costs. Copies (1*s.* 6*d.*) may be had from H.M. Stationery Office.

Diary of the Week

DEC. 10 TO 16

Monday, 11th

ROYAL COLLEGE OF SURGEONS OF ENGLAND, Lincoln's Inn Fields, W.C.2
5 P.M. Sir Wilfrid Le Gros Clark: The Sorting Principle in Sensory Analysis as Illustrated by the Visual Pathways. (Edridge-Green lecture.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON, Ducane Road, W.12
4 P.M. Dr. J. F. Goodwin: Pulmonary Vascular Disorders.

ROYAL SOCIETY OF MEDICINE, 1, Wimpole Street, W.1
5.30 P.M. *Library* (*Scientific Research*). Dr. Neil Orr: Life and Work at an Antarctic Sledging Base.

Tuesday, 12th

BRITISH POSTGRADUATE MEDICAL FEDERATION
5.30 P.M. (London School of Hygiene and Tropical Medicine, Keppel Street, W.C.1.) Dr. I. D. P. Wootton: Retention of Aromatic Compounds in Acute Renal Failure.

ROYAL SOCIETY OF MEDICINE
5.30 P.M. *Experimental Medicine and Therapeutics.* Prof. J. R. Squire, Dr. J. F. Soothill, Dr. F. O. MacCallum, Prof. N. H. Martin: Hypogammaglobulinæmia.
8 P.M. *Psychiatry.* Dr. Eliot Slater, Dr. A. W. Beard: Schizophrenic-like Psychosis of Epilepsy.

ST. MARY'S HOSPITAL MEDICAL SCHOOL, W.2
5 P.M. Mr. Aleck Bourne: Amenorrhœa, its Causes and Significance.

ROYAL ARMY MEDICAL COLLEGE, Millbank, S.W.1
5 P.M. Dr. Nigel Compston: Megaloblastic Anæmias.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE, 28, Portland Place, W.1
5.30 P.M. Sir Christopher Andrewes: Common Cold—Background. (First of three Harben lectures.)

Wednesday, 13th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Dr. Imrich Friedmann: Electron Microscopy. (Erasmus Wilson demonstration.)

POSTGRADUATE MEDICAL SCHOOL OF LONDON
2 P.M. Dr. W. W. Payne: Biochemistry in the Newborn.

INSTITUTE OF DISEASES OF THE CHEST, Brompton, S.W.3
5 P.M. Dr. Howard Nicholson: Early Diagnosis of Bronchial Carcinoma.

ROYAL FREE HOSPITAL, Gray's Inn Road, W.C.1
5.15 P.M. Dr. R. A. Womersley: Magnesium Metabolism.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5.30 P.M. Sir Christopher Andrewes: Common Cold—Recent Laboratory Work. (Second of three Harben lectures.)

MANCHESTER MEDICAL SOCIETY
5 P.M. (Medical School, University of Manchester.) *Pathology.* Dr. J. O. Tobin: Live or Dead Poliomyelitis Vaccines?

Thursday, 14th

ROYAL COLLEGE OF SURGEONS OF ENGLAND
5 P.M. Prof. William Gissane: Basic Surgery of Major Injuries of the Motorways. (Robert Jones lecture.)

INSTITUTE OF CHILD HEALTH, THE HOSPITAL FOR SICK CHILDREN, Great Ormond Street, W.C.1
5.30 P.M. Dr. Alvar Swensson (Stockholm): Respirator Treatment for Children.

ROYAL INSTITUTE OF PUBLIC HEALTH AND HYGIENE
5.30 P.M. Sir Christopher Andrewes: Common Cold—Epidemiology and Possibilities of Control. (Last of three Harben lectures.)

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE, 26, Portland Place, W.1
7.30 P.M. Dr. F. I. C. Apted: Sleeping Sickness in Tanganyika, Past, Present and Future.

Friday, 15th

ROYAL SOCIETY OF MEDICINE
3.30 P.M. *Radiology.* (Joint meeting with the British Institute of Radiology and the Faculty of Radiology.) Dr. John Hodson, Dr. David Sutton: Hypertension. (Opening of two-day meeting.)